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Research paper

Systems approach for classifying the response to biological therapies in patients with rheumatoid arthritis in clinical practice

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ABSTRACT

Introduction: Biological therapies have greatly improved the treatment efficacy in rheumatoid arthritis (RA). However, in clinical practice a significant proportion of patients experience an inadequate response to treatment. The aim of this study is to classify responding and non-responding rheumatoid arthritis patients treated with biological therapies, based on clinical parameters and symptoms used in Western and Chinese medicine.

Methods: Cold and Heat symptoms accessed by a Chinese medicine (CM) questionnaire and Western clinical data were collected as baseline data, before initiating biological therapy. Categorical principal components analysis with forced classification (CATPCA-FC) approach was applied to the baseline data set to classify responders and non-responders.

Results: In this study, 61 RA patients were characterized using a CM questionnaire and clinical measurements. The combination of baseline symptoms ('preference for warm food', 'weak tendon severity') and clinical parameters (positive rheumatoid factor/anti-cyclic citrullinated peptide antibody, C-reactive protein, creatinine) were able to differentiate responders from non-responders to biological therapies with a positive predictive value of 82.35% and a misclassification rate of 24.59%. Adding CM symptom variables in addition to clinical data did not improve the classification of responders, but it did show 8.3% improvement in classifying non-responders.

Conclusions: No significant differences were found between the three classification models. Adding CM symptoms to the clinical parameters in the combined model improved the classification of non-responders. Although this improvement is not significant in the current study, we consider it worthwhile to further investigate the potential of adding symptom variables for improving treatment efficacy.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that results in a systemic inflammation, affecting 0.5% to 1% population in Northern Europe and North America [1]. The pathogenesis of RA is not defined as yet, but there is no doubt that complex immune responses are highly related to inflammation and joint erosion [2]. In the late 1990s, tumor necrosis factor (TNF) inhibitors were introduced for the treatment of RA, followed by other kinds of biological agents including the anti-CD 20 agent, IL-6 inhibitor etc. By targeting cell-surface receptors or intracellular pathways, biological agents show powerful capabilities in the modulation of the immune response [3–5]. Compared to the conventional RA medicines, biological agents can not only reduce disease activity but also decrease or prevent radiographic progression in RA [6].

Biological therapies can greatly improve the treatment outcome in

Abbreviations: RA, rheumatoid arthritis; CM, Chinese medicine; TNF, tumor necrosis factor; DMARDs, disease, modifying anti-rheumatic drugs; EULAR, European League Against Rheumatism; DAS28, disease activity score in 28 joints; BMI, body mass index; ROC, receiver operator characteristic; TJC, 28 tender joint count; SJC, 28 swollen joint count; VAS, 100 mm visual analogue score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibody; CATPCA, categorical principal components analysis; FC, forced classification; LOOCV, leave-one-out cross-validation

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RA, but there is a significant proportion of patients who have an inadequate response. Approximately 30% of the RA patients failed to respond after (at least) three-month biological treatment [7]. For these non-responders this problem is compounded by high financial cost and significant side effects. Additionally in clinical practice for RA treatment, a biological agent is recommended only if the treatment outcome of non-biologic therapy is not reached with 6 months [8]. Therefore, the opportunity to control the erosion of joints in early RA might be missed, further affecting the long-term outcomes of RA [9]. Hence, it is necessary to better target this medication to patients who will benefit from the biological therapies [10], and to develop more personalized medication based a novel diagnostic principle.

As a practical medicine, Chinese medicine (CM) has a long history of development and optimization through observation in daily practice. Especially for complex diseases, CM could provide new possibilities for subtyping patients by pattern diagnosis [11]. In CM, RA is defined as a Bi-syndrome [12]. Bi-syndromes consist of multiple subtypes based on symptom patterns, including two basic patterns—'Cold' and 'Heat'. For each pattern of RA, there is a different treatment strategy in CM [13]. We previously reported differences in biological mechanisms between Cold and Heat RA patients, determined by metabolomics measurements of plasma and urine samples as well as gene expression analysis of CD-4 T-cells [14,15]. A large literature mining study suggests that Cold type of diseases is related to hormone disturbances whereas immune systems disturbances are Heat type related [16]. Therefore, we hypothesize that the Cold or Heat patterns may be associated with the response to biological therapies (such as TNF-α blockers) of RA patients.

There is already some evidence that response to therapy is different between Cold and Heat RA patients. In a study by Lu et al. a difference between cold and heat pattern RA patients in ACR 20 response to diclofenac, methotrexate and sulfasalazine therapy in 12 and 24 weeks is reported [42]. Another study reports optimal symptom combinations of RA patients with a good response to a similar therapy [43]. Therefore, the response to biological therapies such as TNF-α blockers might also be different depending on CM pattern diagnosis.

According to CM, Cold or Heat diagnosis is based on integrating corresponding symptoms. However, in most cases patients diagnosed with Cold RA could also show Heat RA related symptoms, besides dominant Cold symptoms; or the other way around with RA Heat patients. Thus, it is difficult to find patients with exclusively Cold or Heat patterns in practice. Therefore, in the present study we focused on the individual Cold and Heat symptoms instead of patterns. Symptoms, which are important for the evaluation of patients' quality of life and disease burden, are more and more used as patient-reported outcome measures for the evaluation of treatment effects in clinical studies [17,18]. Many factors from clinical and lab tests have been already reported as predictors/biomarkers of patients' response to biologic agents [19–22], but there is no study including baseline symptoms as potential markers.

In this study we used Eastern and Western diagnostic principles, including Cold and Heat symptoms as well as other baseline disease characteristics, to classify response to biological therapy in patients with RA. If we are able to better classify non-responders and responders at the start of biological therapy, patients can be treated with the best available drugs timely, avoiding side effects and unnecessary financial cost caused by trial-and-error practice.

2. Materials and methods

2.1. Study design and participants

RA patients were selected from the observational BiOCURA study (Biologicals and Outcome, Compared and predicted in Utrecht region, in Rheumatoid Arthritis), in which patients with RA starting a biological therapy were recruited (Dutch registry number (ABR) NL23830.041.08). There was no particular intervention in this purely observational study. After three months of treatment with one of the following biological agents: Etanercept, Adalimumab, Golimumab, Certolizumab pegol, Rituximab, Abatacept or Tocilizumab. The outcome of the therapy was assessed according to EULAR response criteria. Re-inclusion after switching to a different biological agent was possible. The type of biological agent provided to each of the patients was decided by their own clinician as is done in routine clinical practice. The study was approved by the Medical Ethical Committee of UMC Utrecht (METC registration number 08-235) and all subjects gave their written informed consent for participation in any procedure specifically for the study. Our study was restricted to the BiOCURA patients who completed a CM questionnaire at baseline.

2.2. Symptom questionnaire

This questionnaire was designed to measure symptoms based on a CM perspective of Cold/Heat patterns on arthritis, which was developed and tested recently [14]. The same questionnaire was used in the present study except translated into the Dutch language, which consists of 57 items separated into five categories (breathing, digestion, climate, quality of the symptoms and pain). Most of the questions are with a Likert-scale, evaluating the severity and the frequency of symptoms from score 1 to 7. Score 1 was interpreted as never or not and score 7 was very severe or very often. The remaining questions were in yes/no format. The questionnaires were completed before initiating of biological therapy and used as baseline symptom data.

2.3. Demographics and clinical parameters

Before starting biological therapy, clinical parameters and demographic characteristic were obtained as baseline clinical data. The following demographics and clinical parameters of patients were collected at baseline: gender, age, body mass index (BMI), disease duration, smoking status, alcohol consumption, biological naivety, concomitant DMARDs, 28 tender joint count (TJC), 28 swollen joint count (SJC), 100 mm visual analogue score (VAS), disease activity score in 28 joints (DAS28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, hemoglobin, alanine aminotransferase (ALT), leukocyte count, rheumatoid factor (RF), platelet count, and anti-cyclic citrullinated peptide antibody (anti-CCP).

After three-month treatment, DAS28 was measured again as present DAS28. By combining the present DAS28 as well as the improvement of DAS28 after three-month treatment, a patient's response to a biological agent can be evaluated according to EULAR response criteria [23]. A good response was defined as a present DAS28 $\leq$ 3.2 with a DAS28 reduction $>$ 1.2, whereas a reduction of DAS28 $\leq$ 0.6 or present DAS28 $>$ 5.1 with a reduction $\leq$ 1.2 was defined as non-response. In between, a reduction $>$ 1.2 with present DAS28 $>$ 3.2 or a reduction between 0.6 and 1.2 with present DAS28 $<$ 5.1 was specified as a moderate response. Since both good-and moderate responders achieve sufficient response, they were combined as responders in the following data analysis [24].

2.4. Data analysis

Firstly, univariate analyses including independent student's *t*-tests, chi-square tests, and Kruskal wallis H tests were applied to compare the differences of baseline clinical and demographic data between responders and non-responders. Subsequently, multivariate analysis was performed on combined data from questionnaires, clinical parameters, and demographic characteristics. Since the combined data sets contained variables with different measurement levels (nominal, ordinal, or numeric) that might be nonlinearly related to each other, categorical principal components analysis (CATPCA) was applied [25].

As a nonlinear principal component analysis technique, CATPCA allows different analysis levels (numeric, ordinal and nominal) for