Clinical Observations

The Extraarticular Symptoms Influence ACR Response in the Treatment of Rheumatoid Arthritis with Biomedicine: A Single-blind, Randomized, Controlled, Multicenter Trial in 194 patients

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Objective: The extraarticular symptoms are important in the pattern differentiation of traditional Chinese medicine (TCM), and the present study is designed in an attempt to find the associations between the extraarticular symptoms and American College of Rheumatology (ACR) Response in 194 cases of rheumatoid arthritis (RA) treated with biomedicine.

Methods: The data were obtained from a randomized clinical trial. One hundred ninety-four RA patients were treated with the biomedical therapy (diclofenec, methotrexate and sulfasalazine). ACR20 response in 24 weeks was used for the efficacy evaluation. Eighteen symptoms (including 13 extraarticular symptoms) that TCM practitioners focus on were collected for exploration on the association between the symptoms and the efficacy of the biomedical therapy with association rules method.

Results: After 24 weeks, a total of 135 patients receiving biomedicine had achieved an ACR20 response. The association rules analysis on each symptom showed that soreness in the waist was more associated with ACR20 response, but with lower support (selected sample size based, 20.10% and 14.95% respectively); cold intolerance and cold joint were found to be associated with ACR20 response with higher support (48.97% and 53.61% respectively), and the confidences (predicted effective rate) were 73.08% and 71.23% respectively. The associations between combination of symptoms (among them, there was at least one extraarticular symptom) and ACR20 response indicated that cold intolerance or cold joint with higher confidence and support were the most important extraarticular symptoms.

Conclusion: The RA patients with “cold intolerance” and “cold joints”, which are the extraarticular symptoms that TCM practitioners focus on, may show higher ACR20 response when treated with the biomedical approach.

Keywords: symptoms; Chinese medicine; rheumatoid arthritis

Rheumatoid arthritis (RA) is a long-term disease that causes inflammation of the joints and surrounding tissues, leading to a wide variety of symptoms and signs. The symptoms in RA are diversified, and can be basically classified into the articular and extraarticular ones. The extraarticular symptoms, such as depression, are associated with inflammation and appear to have independent effects on perceived pain in rheumatoid arthritis. While more extraarticular symptoms, such as intolerant to cold and cold joint, are considered to be most important evidence for Traditional Chinese medicine (TCM) pattern differentiation (similar to diagnosis in biomedicine), which guides TCM therapy in the treatment of disease. The authors’ previous study showed that TCM pattern differentiation based on the symptoms can help identify a subset of rheumatoid arthritis patients that will more likely respond to biomedical therapy, though TCM pattern differentiation is hard to be understood by biomedical scientists. Using statistical tools and modeling techniques, the interesting and hidden rules in the data may be found, and the association rules is one of the important data mining tasks which can reveal the relationships among different items. In this paper, the authors applied the standard data mining technique of the association rules as a basis to explore the clinical trial data on RA patient in order to show the influence of extraarticular symptoms on ACR20 response in the treatment with the biomedical approach.

METHODS

Study Design
This multicenter, randomized, single-blind (patients were unaware of detailed therapy) study, in which the assessors (rheumatologists) blinded, was conducted at 9

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centers in China. The primary endpoint was ACR 20 in 24 weeks. More details about the clinical trial have been reported previously.8

Inclusion Criteria
Men and women, aged from 18 to 70 years, were eligible to participate if they met the American College of Rheumatology (ACR) criteria for RA, with disease duration at least for one year, and the illness condition categorized as Class I, II, or III under ACR guidelines.9 Patients who agree to sign an informed consent were obtained.

Exclusion Criteria
The patients with severe cardiovascular, lung, liver, kidney, hematologic or mental disease, and women who were pregnant, breast-feeding or were planning to be pregnant in the following 8 months were excluded.

Sample Size Determination
The sample size was established by comparing the rates of validity between TCM and Western medicine. In reviewing the literature, the sample size can be calculated by the estimated value of the rate of validity for the formula, 91.11% in the TCM group and 79.00% in Western medicine group (set α=0.05, β=0.10). Sample size was 201 in both groups. And with a dropout rate for follow up as 20%, the sample size for each group was 241 and 482 in the two groups.

Randomization
The patients were randomized by computer using the SZS-12 PRCO PLAN system (Version 6.12 for Windows). The details of the allocation sequence were in a sealed envelope and unknown by the study investigators and the participants. Randomization was designed so that each participant would have a 50% chance of assignment to one of the two groups, and each participant had their own unique code number. Only this number was used to identify the patients’ Case Report Form.

Blinding
As for the different interventions in the trial, some drugs have adverse reactions (such as the effect of Tripterygium torotum on the reproductive system). Case group division is adapted to single-blind method with the therapeutic effects and side effects evaluated by an independent third party. The study was approved by the Ethical Research Committee, Guangdong Provincial Hospital of Traditional Chinese Medicine. Informed consent was obtained from each patient.

Procedures
From February 1997 to November 1997, a total of 522 patients were enrolled into the study. Of these 522 patients, 489 qualified for the clinical study and 437 patients complete the follow up. (Flow Chart 1).

Flow Chart 1. Number and reasons for patients not completing the study.
Trial Profile
Fifty-seven patients withdrawn from the study, 18 due to poor efficacy, 17 according to their request, 5 for other reasons (change job; attending training classes and starting a new job) and 17 because of adverse effects. None of the adverse effects was serious. Of the 437 patients who completed the follow-up, 41 patients who did not receive laboratory examination were not included in the PPSA and X-ray analysis. One hundred ninety-four patients in WM group with a Disease Activity Scores that include different 28-joint (DAS28-3) score of higher than 2.6 were admitted into statistical analysis.

Interventions
Patients in Western medicine-treated group: Biomedical combination therapy using both the nonsteroidal anti-inflammatory drugs (NSAIDs) and the disease modifying anti-rheumatic drugs (DMARDs). Diclofenec (extended action 75 mg tablet) as the NSAID was orally taken once a day after a meal till the acute inflammation was controlled. The DMARDs used were Methotrexate (MTX) and Sulfasalazine (SSZ). MTX was orally taken once a week at a starting dosage of 5 mg with addition of 2.5 mg each week up to 15 mg, and a maintenance dosage from 2.5 mg to 7.5 mg. SSZ was orally taken twice a day from a starting dosage of 0.25 g with the addition of 0.25 g each week, to a maintenance dosage of 0.5 g to 1 g, four times a day.

Measurements
In the 12th week and the 24th week, the ACR20 was recorded and used for the evaluation of efficacy. Efficacy evaluation was done by a third party (rheumatologists at each center) who did not know the biomedical combination therapy.

Within 14 days before randomization, a complete physical examination, medical history, and assessment of 18 symptoms (joint pain, joint tenderness, joint swelling, joint stiffness, cold intolerance, soreness in the waist, frequent urination at night, hot joint, thirsty, fatigue, dysphoria, cold limbs, vexation, fever, weakness in the waist, dizziness, turbid urine in yellow color, numb heavy limbs) typically evaluated by TCM physicians were performed and recorded.

Only patients treated with the biomedical combination therapy were included for analysis in this study. Disease activity was assessed by DAS28-3. Only patients with a DAS28-3 score higher than 2.6 were admitted into statistical analysis.

Safety Analyses
Five hundreds and ten patients were included in the Safety analyses.

Role of the Funding Sources
This study was supported by the National Key Project of the 10th Five-Year Plan. The funding sources had no role in study design; collection, analyses, and interpretation of all data; writing the article; and the decision to submit the manuscript for publication.

Statistics
Sample size for this study was calculated based on an estimate for TCM response rate of 91.11% and WM ACR20 response rate of 79.00% referring to previous clinical literature. The sample size calculation was performed using the formula of proportions under the assumption of a two-tailed test with 80% power and an alpha level of 0.05. The required sample size was therefore 201 cases in each group. The sample size was increased to 241 in each group to allow for withdrawals.

Association rules on SAS 9.1 Enterprise Miner statistical package (Order No. 195557) were used. In this study, the symptoms (including some signs such as joint swelling) were set as items. In order to clarify the rules, the definitions for Support and Confidence are described with the following examples:

Suppose the \{item: symptom A\} ==> Effective as association rule, 39 patients with symptom A have effect, 194 patients got biomedical combination therapy, then the Support is 39/194 = 20.10%.

Suppose the \{item: symptoms A & symptoms B\} ==> Effective as association rules, 28 patients (responsive case number) with symptom A have effect, total 47 patients with symptom A, then the Confidence is 28/47 = 82.98%.

A Chi-Square test is conducted to determine whether the baseline data (gender, age) for RA patients with the symptoms related to 11 association rule are statistically different from what was expected as compared to RA patients without the symptoms related to 11 association rule, which determines whether the implementation (explore the patients with some symptom or symptoms combination) was successful due to process improvements or to chance.

Then, the therapeutic efficacy in 194 RA patients with or without the symptoms related to 11 association rules were compared with Chi Square analysis. A Chi-Square test is conducted to determine whether efficiency for the sample group (with the symptoms related to association rule, rule = 0) are statistically different from what was expected as compared to the group (without the symptoms related to association rule, rule = 1). The goal is to have a P-value that is less than 0.05, which means that there is a less than 5% probability for the results that
could have been produced by chance.

RESULTS
ACR Efficacy Evaluation
Of the 522 patients who underwent randomization, 21 patients were excluded as not meeting the inclusion criteria, and 12 patients were excluded by refusing to participate. 489 were included in the trial, 247 in TCM group, and 242 in biomedical combination therapy group. Baseline characteristics were similar between the treatment groups. Thirty-eight patients in the biomedical combination therapy group dropped out, and a total of 194 patients received for 24 weeks. All the 194 patients treated with the biomedical combination therapy were analyzed. ACR20 response in the 12th week was 36.08%, and ACR20 response in the 24th week was 69.59% (Figure 1).

Figure 1. ACR response in RA patients treated with the biomedical combination therapy for 12 weeks and 24 weeks.

Association between ACR20 Response and the Extraarticular Symptoms
The associations between ACR20 response and single extraarticular symptom were analyzed (rule 1 in Table 1), and the associations between ACR20 response and 2 or 3 combination (of 2 or 3 symptoms) at least including one extraarticular symptom were analyzed (rule 2 to 11 in Table 1).

The first 1 association rule in Table 1 indicated that, with more than 80% confidence, soreness in the waist was more associated with effectiveness. However, the RA patients did not often show single soreness in waist (with support of 20.10%). Cold intolerance and cold joint were found to be associated with ACR20 response with higher support (48.97% and 53.61% respectively), and the confidences were 73.08% and 71.23% respectively. Thus the associations of two or three symptoms with ACR20 response were further explored. From the rule 2 on in Table 1, all rules indicated that cold intolerance or cold joint were the most important extraarticular symptoms, and the ACR 20 response in the cases with diagnostic related articular symptoms combined with these two extra-articular symptoms would be higher than 69.59% (ACR20 response in all 194 patients).

The baseline characteristics (gender, age) showed no significant differences between patients with and without one association rule. The of Chi-Square tests represented the therapeutic efficacy in 194 RA patients all showed significant differences between patients with or without symptoms related to 11 association rules (Table 2).

Table 1. Association rules obtained from the symptoms of RA and ACR response with biomedical combination therapy

<table>
<thead>
<tr>
<th>No.</th>
<th>Association rule</th>
<th>Support (%)</th>
<th>Confidence (%)</th>
<th>Responsive case number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Soreness in waist ( \Rightarrow ) Effective</td>
<td>20.10</td>
<td>82.98</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>Cold intolerance, Joint stiffness &amp; Joint pain ( \Rightarrow ) Effective</td>
<td>20.62</td>
<td>93.02</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>Cold intolerance, Joint stiffness &amp; Cold joints ( \Rightarrow ) Effective</td>
<td>20.10</td>
<td>90.70</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>Cold intolerance &amp; Joint stiffness ( \Rightarrow ) Effective</td>
<td>21.65</td>
<td>87.50</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>Cold intolerance &amp; Joint swelling ( \Rightarrow ) Effective</td>
<td>20.62</td>
<td>86.96</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>Cold intolerance, Joint tenderness &amp; Joint pain ( \Rightarrow ) Effective</td>
<td>27.32</td>
<td>82.81</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>Cold intolerance &amp; Joint pain ( \Rightarrow ) Effective</td>
<td>32.99</td>
<td>82.05</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>Cold intolerance, Joint pain &amp; Cold joints ( \Rightarrow ) Effective</td>
<td>30.41</td>
<td>81.94</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>Cold intolerance &amp; Joint tenderness ( \Rightarrow ) Effective</td>
<td>30.93</td>
<td>78.95</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>Cold intolerance, Joint tenderness &amp; Cold joints ( \Rightarrow ) Effective</td>
<td>28.35</td>
<td>78.57</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td>Cold intolerance &amp; Cold joints ( \Rightarrow ) Effective</td>
<td>45.36</td>
<td>75.21</td>
<td>88</td>
</tr>
</tbody>
</table>

Notes: \( A \Rightarrow B \) means that A is more likely associated with B. The Support is the percentage of responsive cases with the symptom in the total treated cases. The Confidence is the percentage of responsive cases with the symptom in the total cases with the symptom. The ACR20 response after treatment with biomedicine for 24 weeks was 69.59% (in total 194 cases) and the rules with Confidence >70% were included.
Table 2. Therapeutic efficacy in 194 RA patients with or without symptoms related to the 11 association rules

<table>
<thead>
<tr>
<th>No.</th>
<th>Association rule</th>
<th>Symptom</th>
<th>Total</th>
<th>Effective (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>{Soreness in waist} ==&gt; Effective</td>
<td>0</td>
<td>147</td>
<td>65.31</td>
<td>0.0219*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>47</td>
<td>82.98</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>{Cold intolerance, Joint stiffness &amp; Joint pain} ==&gt; Effective</td>
<td>0</td>
<td>151</td>
<td>62.91</td>
<td>0.0002*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>43</td>
<td>93.02</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>{Cold intolerance, Joint stiffness &amp; Cold joints} ==&gt; Effective</td>
<td>0</td>
<td>151</td>
<td>63.58</td>
<td>0.0006*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>43</td>
<td>90.70</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>{Cold intolerance &amp; Joint stiffness} ==&gt; Effective</td>
<td>0</td>
<td>146</td>
<td>63.70</td>
<td>0.0019*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>48</td>
<td>87.50</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>{Cold intolerance &amp; Joint swelling} ==&gt; Effective</td>
<td>0</td>
<td>148</td>
<td>64.19</td>
<td>0.0034*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>46</td>
<td>86.96</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>{Cold intolerance, Joint tenderness &amp; Joint pain} ==&gt; Effective</td>
<td>0</td>
<td>130</td>
<td>63.08</td>
<td>0.0050*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>64</td>
<td>82.81</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>{Cold intolerance &amp; Joint pain} ==&gt; Effective</td>
<td>0</td>
<td>116</td>
<td>61.21</td>
<td>0.0020*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>78</td>
<td>82.05</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>{Cold intolerance, Joint pain &amp; Cold joints} ==&gt; Effective</td>
<td>0</td>
<td>122</td>
<td>62.30</td>
<td>0.0041*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>72</td>
<td>81.94</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>{Cold intolerance &amp; Joint tenderness} ==&gt; Effective</td>
<td>0</td>
<td>118</td>
<td>63.56</td>
<td>0.0230*</td>
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<td></td>
<td></td>
<td>1</td>
<td>76</td>
<td>78.95</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>{Cold intolerance, Joint tenderness &amp; Cold joints} ==&gt; Effective</td>
<td>0</td>
<td>124</td>
<td>64.52</td>
<td>0.0410*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>70</td>
<td>78.57</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>{Cold intolerance &amp; Cold joints} ==&gt; Effective</td>
<td>0</td>
<td>77</td>
<td>61.04</td>
<td>0.0358*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>117</td>
<td>75.21</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Symptom 0=patients with this symptom or symptom combination; Symptom 1= patients without this symptom or symptom combination. *P<0.05

DISCUSSION

The previous study showed that biomedicine therapy was better in treating RA with TCM cold pattern. However, it is really hard for biomedical scientists to understand the meanings of TCM pattern classification, even harder to understand all the TCM focused extraarticular symptoms. Therefore, it would be important to find out the influence of the common TCM focused extraarticular symptoms on the efficacy in the treatment of RA, with the indication and specification for the biomedicine therapy. In the present study, two extraarticular symptoms, that is cold intolerance and cold joint, were found to be related to ACR20 response for the biomedicine combination therapy.

Data mining is a technique for discovering the useful information from large databases. A large database represents a huge amount of information which can be potentially very useful if extracted and summarized correctly, and using the statistical tools and modeling techniques, one can discover the interesting and hidden patterns in the data. Here, the authors applied the standard data mining technique of association rules as a basis to explore the patients’ data. Association rule mining is one of the important data mining tasks which may reveal the relationships among different items. Association rule mining technology is being currently used by a number of medical fields, including gene, clinical, and so on. Thus, the authors think it would be suitable to apply this approach to explore the influence of the symptoms TCM concerned and ACR20 response. In this paper, the writers used the analysis to explore each of the symptoms and the symptom combinations, and found that cold intolerance and cold joint were the most important symptoms associated with the efficacy.

But how to set proper minimum confidence to association rule mining algorithm is a very important issue in applying association rule mining. The association rules are considered interesting if they satisfy both a minimum support threshold and a minimum confidence threshold. Such thresholds can be set by users or domain experts but not a common criterion. There is no general rule to set a proper minimum threshold and the only thing the authors can do is setting minimum threshold by their experience and by characteristic of database. The professional experience includes the relationship between the symptoms and diseases based on TCM theory. Furthermore, all the 194 patients treated with the biomedicine were analyzed, and the ACR20 response in the 24th week was 69.59% (Figure 1). The
authors use data mining in order to explore patient with some combination of symptoms will get higher response. If the writers set higher threshold, they may get too less association rules, so they set minimum confidence as 70% and get 11 rules. The authors considered that these 11 rules could be used for the further discussion but not too much. In this study, the hypothesis is that, given association rules that capture the characteristics of patients. Then, the authors test the therapeutic efficacy in 194 patients whether have significant differences between patients with or without symptoms related to the 11 association rules that they have captured. That means the therapeutic efficacy in patients with different characteristics is different. And the authors will verify their hypothesis by carrying out next clinical trials and other methods.

It has been proved that one of the important symptoms for TCM pattern differentiation could influence the efficacy of therapies, and that some extraarticular or manifestations, such as inflammatory responses in other organs, may lead RA into different progressive way that need different therapeutic approaches. In TCM, all the symptoms and signs (including tongue appearance and pulse feeling, which will not be discussed here because of their complexity in understanding from the view of biomedicine), especially those extraarticular symptoms which exist widely in RA patients but not emphasized by biomedicine, are the important information for TCM pattern differentiation. The previous results showed that RA patients with some specific extra-articular symptom or symptom combination could be treated in more efficient way with a therapeutic method of either biomedicine or TCM. And the results supported that the efficacy of biomedical combination therapy would be better if only used in the RA patients with cold intolerance and cold joint. Few of the rheumatologists care about the extraarticular symptoms in clinical practice in biomedicine, but the TCM doctor does care about it. The writers’ findings indicate that some extraarticular symptoms should be taken into consideration for the indication and specification of a therapy or an anti-rheumatic drug.

The RA patients with intolerance to cold and cold joints, which are the extraarticular symptoms focused by TCM, may show higher ACR20 response when treated with the biomedical approach. The results further suggested that the extraarticular symptoms that TCM practitioners focus on would be useful for specifying the indication of the biomedicine therapy.

REFERENCES


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