The Effect of Cabergoline on Clinical and Laboratory Findings in Active Rheumatoid Arthritis

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Dear Editor,

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder affecting approximately 1% of the world’s population (1). In recent years, a number of biological agents have been developed that may ameliorate the symptoms of RA and other ailments; however, their cost and potential side effects prohibit widespread use. Dopamine agonists such as bromocriptine and cabergoline decrease prolactin (PRL) synthesis and secretion by binding to cell surface dopamine receptors (2).

PRL is secreted primarily by the anterior pituitary gland but also by immune cells, and it has been shown that it can stimulate some immune cells by binding to prolactin receptors on the cells (3). PRL receptors are exclusively expressed on fibroblast-like synovial cells and lymphocytes infiltrating into the synovium of patients with RA (4). It has been demonstrated that PRL can enhance synovial cell proliferation in RA. To date, there have been four open trials that have studied the use of bromocriptine (5-8) and one case report on the use of cabergoline (9) in RA treatment. Cabergoline is an ergot dopamine agonist that is administered once or twice a week and has much less tendency than bromocriptine to cause nausea (10).

The present study was a pilot randomized, double-blind, crossover clinical trial, carried out from September 2009 to May 2010 on 10 female patients with active rheumatoid RA who had been referred to a rheumatology clinic in Sari, Iran. RA was defined according to the American College of Rheumatology (ACR) 1987, and criteria for disease activity included the existence of 4 swollen joints plus 2 of the following:

1) Existence of 6 tender joints
2) Morning stiffness lasting more than 30 minutes
3) An erythrocyte sedimentation rate (ESR) greater than 28 mm/h (11, 12)

The patients suffered from active RA despite receiving prednisolone and disease-modifying antirheumatic drugs (DMARDs) for at least 3-6 months. The study was approved by the ethics committee of Mazandaran University of Medical Sciences and was recorded in the Iranian Registry of Clinical Trials (IRCT) (code: IRCTI38802061828N2). All patients signed informed consent forms. Patients with psychosis, or who were pregnant or lactating, were excluded from the study. Patients continued taking previously prescribed drugs at the same dosage throughout the trial. Patients were divided randomly into two groups, one to receive 1 mg/wk cabergoline (Pharmacia and Upjohn S.P.A., Italy) first and one to receive placebo (Pharmacy Faculty, Sari, Iran) first. The two groups were similar in terms of disease duration and activity, and the main antirheumatoid therapy used.

In the first step, patients took cabergoline or placebo for 3 months; then, after a 1-month washout period, they used the other drug for another 3-month period. Changes in disease activity were noted at the beginning of the study and at the third, fourth, and seventh month of treatment, and possible side effects were recorded. Statistical analysis was performed by t-test for quantitative variables; a matched-pairs t-test was used for comparison between before and after intervention. Nonparametric statistical analysis was performed by Wilcoxon signed-rank and Friedman exact tests for comparison between before and after intervention. Of the 10 patients who entered this trial, 9 completed the trial. One patient in the first group was excluded because of complaints of vertigo and vomiting. At the beginning of the trial, the mean age of the patients was 55.6 ± 9.5 years; mean disease duration was 12.1 ± 6.0 years; duration of morning stiffness was 30.5 ± 41.2 min; tender and swollen joint counts were 7.4 ±
2.8 and 5.1 ± 1.8, respectively, and patient assessment of pain and global assessment of disease activity were 6.4 ± 3.0 and 5.5 ± 2.9, respectively, on the visual analog scale (VAS). The mean serum PRL level was 9.4 ± 7.0 mIU/L and the mean ESR was 35.0 ± 14.4 mm/h. After intervention with cabergoline, mean PRL decreased from 10.6 ± 4.3 to 6.4 ± 5.8 ($P = 0.188$), and with placebo it increased from 9.9 ± 10.7 to 15.0 ± 8.4 ($P = 0.375$). A comparison of changes in disease activity with cabergoline and placebo is shown in Table 1.

In this study, improvement in tender and swollen joint count and patient assessment of pain and global assessment of disease activity were significant when patients were treated with cabergoline. PRL is secreted not only by the anterior pituitary gland but also by immune cells that may have a small effect on total serum PRL level but may have a significant effect on the immunomodulatory system. Thus, improvement in RA activity with cabergoline may result from significant suppression of PRL secretion by immune cells without a significant change in serum PRL levels, as was found in this study. In contrast, Dougados and coworkers found no difference in clinical and laboratory measures of disease activity with use of bromocriptine in 6 RA patients (5). In another study of 30 patients with active RA, Marguerie et al. demonstrated some clinical improvement (comparable to penicillamine) using bromocriptine (8). Mader and Figueroa et al. have also demonstrated some clinical improvement with the use of bromocriptine (6, 7).

Erb and coworkers have reported a patient with severe uncontrolled RA that improved rapidly after cabergoline treatment for coincidental hyperprolactinemia (9), and Eijsbouts et al. tried quinagolide for 6 months; however, despite suppression of PRL level, there was no improvement in clinical or laboratory findings of disease activity (13). This study is the first clinical trial to examine the use of cabergoline in RA. It was a small pilot study, and we recommend future studies with a greater number of subjects and using different dosages and intervals of PRL inhibitors, particularly cabergoline. Two of the patients in our trial did not have a good tolerance with 1 mg/wk cabergoline, thus we suggest administering it at a lower dosage 2 times a week. Cabergoline is long acting, its mode of administration and cost are acceptable, and associated complications are few and mild. These factors, we believe, provide a good rationale for further studies on the use of cabergoline in RA and other rheumatologic disorders that formerly have shown improvement using dopamine agonists.

**Keywords:** Arthritis, Rheumatoid; Prolactin; Cabergoline; Dopamine Agonist

### Financial Disclosure

[Will be written by authors]

### References


### Table 1. Comparison of Changes in Disease Activity with Use of Cabergoline and a Placebo

<table>
<thead>
<tr>
<th></th>
<th>Before Cabergoline, Mean ± SD</th>
<th>After Cabergoline, Mean ± SD</th>
<th>$P$ value</th>
<th>Before Placebo, Mean ± SD</th>
<th>After Placebo, Mean ± SD</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness, min</td>
<td>17.8 ± 28.5</td>
<td>25.6 ± 45.7</td>
<td>1.000</td>
<td>18.3 ± 29.5</td>
<td>30.0 ± 78.8</td>
<td>1.000</td>
</tr>
<tr>
<td>Tender joint count, No.</td>
<td>6.7 ± 3.6</td>
<td>2.7 ± 2.3</td>
<td>0.011</td>
<td>3.9 ± 4.4</td>
<td>3.0 ± 2.9</td>
<td>0.594</td>
</tr>
<tr>
<td>Swollen joint count, No.</td>
<td>4.1 ± 2.6</td>
<td>2.0 ± 1.6</td>
<td>0.031</td>
<td>2.7 ± 3.4</td>
<td>1.8 ± 2.8</td>
<td>0.344</td>
</tr>
<tr>
<td>Patient assessment of pain $^a$</td>
<td>5.6 ± 3.5</td>
<td>3.2 ± 2.4</td>
<td>0.047</td>
<td>4.9 ± 3.4</td>
<td>4.1 ± 3.6</td>
<td>0.438</td>
</tr>
<tr>
<td>Patient global assessment of disease activity $^a$</td>
<td>4.67 ± 3.2</td>
<td>2.6 ± 1.8</td>
<td>0.516</td>
<td>4.2 ± 3.3</td>
<td>3.8 ± 3.7</td>
<td>0.625</td>
</tr>
<tr>
<td>ESR, mm/min</td>
<td>41.0 ± 18.6</td>
<td>29.8 ± 16.1</td>
<td>0.156</td>
<td>24.7 ± 18.3</td>
<td>30.7 ± 23.7</td>
<td>0.438</td>
</tr>
</tbody>
</table>

$^a$ On the visual analog scale (VAS)