July 11, 1988

Mr. Perry A. Chapdelaine, Sr.
Executive Director/Secretary
The Rheumatoid Disease Foundation
Route 4, Box 137
Franklin, TN 37064

Dear Mr. Chapdelaine:

This letter is to thank you for your letter of 3-27-88 and provide a final written report to the Foundation concerning our double-blind placebo controlled study of Clotrimazole in the treatment of rheumatoid arthritis. Also enclosed is a copy of Dr. Dennison's abstract presented at the ARA meeting in Houston for which the reference is Arthritis Rheum 31:S53, 1988. I am sending copies of these documents to Dr. Paul Pybus, Dr. Bradley Wells, Mr. Paul Spikerman, and Dr. J. Kiffin Penry, and I want to thank everyone concerned for their support, professionalism, and forbearance in allowing us to work through the data concerning this interesting study. I certainly plan to keep everyone concerned informed should further publications arise from this worthwhile study, but I wanted your group to have the more detailed data than was available in the abstract as a final written report and am therefore sending this to you at this time. I should mention that Dr. John Simoons is interested in receiving this data, but I have been reluctant to send him data other than that which is published, and therefore in the public domain, because of your letter of 1-2-86 asking that I refrain from communicating such data with him. I will of course be happy to communicate the data to him or will be happy for you to do so if you and the Foundation feel such communications are now in order.

Thank you again for your professionalism in handling all aspects of the study.
Mr. Perry A. Chapdelaine, Sr.
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I will look forward to further communications concerning areas of mutual interest.

Yours truly,

[Signature]
Robert Turner, M.D.

RT/mam

Enclosure

cc: Dr. Bradley Wells - Biostatistician, Research & Prevention Biometry
    Mr. Paul Spiekerman - Miles Pharmaceutical
    Dr. J. Kiffin Penry - Chairman, Clinical Research Practices Committee
    Dr. Paul K. Pybus - Chief Medical Advisor, Rheumatoid Disease Foundation
    Dr. William Dennison

tocorticosteroids (CS) exert profound effects on lymphocytes, and formation of specific proteins (IgG) which inhibit cell proliferation and interferon γ (IFN-γ) production. We used an in vitro assay to compare lymphocyte antibody (AL) and high dose oral CS in RA patients.

To determine whether AL are functionally important, we assessed 12 of 18 AL in the presence and absence of lymphocyte antibody inhibition by the use of semi-quantitative analysis in RA patients exhibiting normal or normal AL. The AL were assayed in HI and matched sera samples for suppression of AR and AL, and AL responses. Peripheral blood lymphocyte (PBL) lines were assessed before and after CS infusion, using standard CT and mononuclear antibody immunomodulation techniques. Patients with normal AL showed a marked reduction of total IL and IgG, before CS; 0.80 x 10^9/L before CS; 0.95 x 10^9/L after CS, with a particularly high helper-inducer cell remaining unaffected. Anti-corticotropin antibodies may impede CS-induced peripheral blood lymphocyte function, especially with no change in the helper-inducer cell ratio. These reduced CS effects in vivo may be due to anti-IgG and may be relevant in patients with steroid resistance in RA.

A93

SEVERE INTERMITTENT 2 RECEPTOR LEVELS REFLECT ACTIVITY OF RHEUMATOID ARTHRITIS. D.R. Ciesielski, D.R. Ehrmann and D.A. Horvitz UBC School of Medicine, VGH, Vancouver, BC.

Increased levels of serum TNFα receptors (2R) are definitive in patients with rheumatoid arthritis characterized by immune system activation. Here we determine the relationship between 2R and activity of rheumatoid arthritis (RA). 18 patients with RA treated with aspirin, HCl (Theraflexin) were studied for 16 to 52 weeks and were divided into 2 groups according to clinical improvement. Before the study, the 2R levels in RA patients were 70 ± 62 u/mL vs normals <300 u/mL). In 8 patients who improved after Theraflexin, both the Pain/Temperature (P/T) index and RA indices were reduced by 84% over 24 weeks. In comparison, with no change in the P/T index, 2R increased from 70 to 500 u/mL. In 8 responders, there was a strong correlation between 2R and the P/T index (r = 0.74). In those patients that improved there was a strong correlations between 2R and joint swelling, grip strength and morning stiffness, but not with changes in walking time or global assessment. In two cases a rebound increase in the P/T index and the clinical status occurred. There were no significant correlations between measures of RA activity and the Westergren ESR. The strong relationship between 2R and various indicators of rheumatoid arthritis activity in patients studied sequentially suggests that 2R may be an especially useful serological marker of disease activity.

A94

CLOTRIMAZOLE (C) VERSUS PLACEBO (P) IN RHEUMATOID ARTHRITIS (RA). William R. Gionfriddo, Robert A. Turner, June A. Johnson, Bradley Wells, Bowman Gray School of Medicine, Winston-Salem, NC.

This is the first P controlled double-blind trial using the inductive C to treat the RA. Thirty patients (RA) (64) of patients were enrolled to provide a power 20% (possibility of false negative result 20%) using observations from a previous study with immunomodulating agents at the dose of 0.3 mg/kg of an RA patients with active classical or definite RA were randomized and given either 200 mg/kg/day 2 days per week of C or a matching P. Thirty patients in the RA group and 24 patients in the RA group were given a 4-week trial of therapy. The RA group showed significant (P < 0.05) improvements in grip strength (x̄±SEM=125.0±14.3 vs 130.8±14.5). Joint count (27±1.9) decreased in RA patients but increased in P patients. The RA group showed a significant (P < 0.05) increase in the occurrence of upper 52 (23 vs. 14), GU (13 vs. 6) and CWS (13 vs. 5) symptoms. There was no difference in the occurrence of symptoms described as Rheumatoid-Like reactions. This study, using a placebo group and an adequate patient population was designed from previous studies, showed statistical evidence of toxicity but not efficacy for C in the treatment of RA.

A95

IN VITRO EFFECTS OF PROTEINASE METABOLITES ON HUMAN CELLULAR FUNCTION. S Rusev, M J Donovan-Brand, and L Adams. University of Cincinnati Medical Sciences Center, Cincinnati, OH (45267).

Drug-related lupus may follow procainamide (PA) administration. The exact mechanism is unknown but recent studies suggest that metabolites of PA, hydroxyamine (PMA) and a nitric oxide (NO-PA) may be responsible. To evaluate the effect of PMA and NO-PA on cellular function in vitro, varying concentrations of PMA (2-75 uM) and NO-PA (1-13 uM) were preincubated with PBL (CMI) or cultured with PBMs from 26 normal subjects for varying times intervals. PBL, PA and cells alone were studied for 30 minutes. Lymphocytes were cultured for 3, 5 or 7 days with mitogens and lymphocytes measured by [3H]-TdR uptake. Cell surface immunoglobulin (Smg) and generation of T-cell subsets (T-helper cells) were also studied for 30 minutes, flow cytometry; antibody synthesis, IL-1 production and the effect of metabolites on the release of oxygen free radicals by phagocytic cells were assessed by assays for TNF-α, IL-1 and IL-6 by specific antibodies detected by thyrosine blue exclusion. Results showed cytokotoxicity and suppression of [3H]-TdR uptake with both metabolites at high concentrations and generation of IL-1 and TNF production at both lower concentrations of PA. Pre-treatment of the PB with ascorbic acid or a carbon monoxide gas to exposure to PMA abrogated or reduced the ectosaminoglycan formation and restored the suppression of TNF-α, IL-6 and IL-1 production. Production of lymphokine-activated killer cells (LAK) and suppression of T-cell mediated proliferation were also observed. These results indicate that PMA and NO-PA have immunomodulating properties. Studies are currently underway to evaluate the role of these metabolites on the induction of autoimmunity.
Abstract

Seventy-three patients with rheumatoid arthritis were randomized in a double blind study to receive either clotrimazole (20 mg/kg/day) two days a week for 12 weeks or matching placebo. Patients receiving clotrimazole had significant improvements (p<0.05) from baseline in measurements of grip strength, joint count, and patient assessment of pain, but did not improve significantly more than patients on placebo. More adverse experiences occurred in patients taking clotrimazole with gastrointestinal complaints predominating and nine patients discontinued therapy because of these.

Introduction

Clotrimazole [1-(0-chloro-a, a-diphenylbenzyl)imidazole] is an imidazole derivative which is utilized medically primarily for its anti-mycotic effects as a topical treatment for vulvovaginal and oral candidiasis (1). Clotrimazole and other imidazoles have also been shown to have immunomodulating properties such as a dose-dependent inhibition of PMN chemotaxis (2) and inhibition of lymphocyte stimulation by phytohemagglutinins, concanavalin-A and pokeweed mitogen (3). Imidazoles such as cimetidine (4), phenytoin (5), metronidazole (6), levamisole (7), fenflumizole (8), imidazole-2-hydroxybenzoate (9), tiflamizole (10), and clotrimazole (11, 12) have been studied in the treatment of rheumatoid arthritis with mixed results. After the report of an encouraging but uncontrolled study, clotrimazole was compared to ketoprofen in a controlled study by Wotjulewski, et al (12). "Up to 80 mg/kg/day of clotrimazole" was given orally for eight weeks, and although there was a trend in favor of the clotrimazole group during the second month, only one parameter reached statistical significance. Adverse effects were more common in the clotrimazole group and 7/24 patients in that group withdrew.

Our study was designed to assess the efficacy and safety of a lower dose of clotrimazole in the treatment of rheumatoid arthritis.
Materials and Methods

A total of 73 adult patients from the Rheumatology Clinics at North Carolina Baptist Hospital were entered into the study. Eligibility required either definite or classical rheumatoid arthritis by the ARA criteria. Active disease was defined by the presence of three of the following: number of tender or painful joints $\geq 6$, number of swollen joints $\geq 3$, duration of morning stiffness $\geq 3/4$ hour, or Westergren erythrocyte sedimentation rate (ESR) $> 28$ mm/hr.

All patients signed informed consent documents as approved by the local Clinical Research Practices Committee. Patients were excluded if signs or symptoms of other rheumatic diseases were present, as were patients with active peptic ulcer disease, gastritis, or other important GI diseases, cirrhosis, liver enzyme abnormalities $> 20\%$ above the upper limits of normal, or any active systemic disease not well controlled by medications or potentially causing a problem to the patient. Pregnant or lactating females and premenopausal females not following acceptable birth control methods were excluded as well as patients treated with corticosteroids or second line agents such as gold, Penicillamine, antimalarials, or cytotoxic drugs. Stable NSAID therapy was allowed.

Patients were randomized to two double blinded treatment groups. They took either clotrimazole in 250 mg. compressed/scored tablets (provided by Miles Pharmaceuticals, West Haven, CT) or an identical placebo tablet in a dose of 20 mg/kg/day in four divided doses for two consecutive days per week for 12 weeks. For inclusion in the efficacy analysis, a patient had to complete at least four weeks of therapy; all patients were included in the adverse experiences analysis.

After the initial history, physical, and laboratory analyses patients were assessed on a weekly basis. Hours of morning stiffness, grip strength, total joint count, 10 point patient and observer visual analogue scales, and weekly stool hemoccult cards were obtained at each visit. Automated serum chemistries
(SMAC), urinalysis, and CBCs were obtained every other week and a rheumatoid factor (RA latex) and ESR were obtained on the first and the twelfth visits or at drop-out. A modified rheumatoid activity index (MRAI) was calculated as previously described (13).

Adverse experiences were defined as untoward signs and symptoms which could in any way be related to drug administration. A question was posed to the patient "How do you feel?" on each visit and the answer recorded. These were later reviewed and categorized by the investigator prior to unblinding. If a patient withdrew prior to study completion, an effort was made to determine the reason for drop-out. A history and physical examination and laboratory assessments were performed at dropout or at study completion.

Statistical Considerations. Estimation of the required sample size was made using data on variability from from a recent six month protocol comparing 500 mg/day Penicillamine with up to 100 mg/day Azathioprine. These indicated that for a Type I error equal to 0.05 (two tailed t test), a power of 0.80, and true difference between groups in initial to final MRAI of 11, 32 patients per group would be needed.

Measurements in Table 1 were used to evaluate efficacy. Paired t statistics were calculated to test average changes within treatment groups. Differences between average changes for treatment groups were tested with a two sample t test. Chi square analyses were performed on adverse experience data. No adjustments were made for multiple comparisons.

Results

A total of 73 patients were enrolled in this study, 37 in the placebo group and 36 in the clotrimazole group. The patients in each group were well matched with respect to disease duration (\bar{x} of each group = 112 months), age (\bar{x} of each group = 51 years) and the male/female ratio. Six patients in the clotrimazole group and three patients in the placebo group did not complete four weeks of
treatment and were excluded from the efficacy analysis leaving 30 and 34 patients in the respective groups. When considering initial clinical measurements for these patients (Table 1) there was a significantly a higher initial ESR (51 mm/hr vs. 35 mm/hr) (p<0.025) for the clotrimazole patients. Differences between groups in the other entry parameters were not significant.

Both clotrimazole and the placebo groups had significant improvements in grip strength (p<0.05 and p<0.025) (Table 1). The clotrimazole group also showed significant (p<0.05) improvements in joint count and patient assessment of pain. Measurements of ESR, RA latex, and MRAI showed improvements for the clotrimazole group but these were not significant. There were no significant differences between changes within the clotrimazole group compared to changes within the placebo group. No significant changes were observed in white blood cell counts either within or between groups. Additional analyses compared those clotrimazole patients who completed a 12 week course (n=19), to those who completed 4-8 weeks (n=9); also placebo patients completing 12 weeks (n=26) were compared with the corresponding clotrimazole group (n=19) and no significant differences were found.

Withdrawals. In the placebo group, 11 patients withdrew prior to the completion of the study, while 18 patients in the clotrimazole group withdrew (Table 2). Clotrimazole dropouts occurred somewhat earlier on average than placebo dropouts. Lack of effect as perceived by the patient was given as the reason for withdrawal in five patients in both groups. In the placebo group, one patient developed a skin rash and was withdrawn from the study, while 9 patients in the clotrimazole group were withdrawn because of adverse experiences. Only 4/9 patients in this group withdrew within the first four weeks. Reasons included: burning upon urination, decreased mental alertness, upper gastrointestinal tract symptoms, and elevated liver enzymes. Other adverse experiences occurred in the nine patients and 19 of 89 total occurrences were in these patients. Five patients in the placebo group and four patients in
the clotrimazole group were either lost to follow up or withdrew from the study because of an intercurrent illness. In addition, there were more adverse experiences in the clotrimazole patients, both among those who withdrew prior to 12 weeks and those who completed the study.

Adverse Experiences. Adverse experiences were common in both groups with 89 separate occurrences in the clotrimazole group and 60 in the placebo group (Table 3). Upper gastrointestinal symptoms were the most frequent adverse experience in both groups with a significantly greater (p<0.05) number of occurrences in the clotrimazole group. Approximately 64% of patients in that group complained of nausea, vomiting, epigastric burning, indigestion, anorexia or regurgitation. Complaints of burning upon urination (genitourinary) were more common (p=0.053) in the clotrimazole group, as were CNS adverse experiences (p<0.025) including decreased mental alertness and taste abnormalities. Liver function test elevation (i.e. SGOT, SGPT, GGT) were more frequent in the clotrimazole group but this was not significantly different. Only one patient in the clotrimazole group was withdrawn because of elevated LFTs. A total of five patients in both groups had abnormal liver function tests which resolved while on treatment. Five patients in the clotrimazole group had sustained mild elevation in LFTs which resolved after completion of the study compared to three patients in the placebo group. No patient in either group had serious long term morbidity resulting from treatment.

Discussion

Wyburn-Mason (11) reported dramatic and essentially curative results in an uncontrolled study using clotrimazole at the daily dose of "25-100 mg/kg body weight" for less than one month. He also noted similar results with only 10-12 mg/kg. A controlled study (12) attempted to confirm this using 40 mg/kg/day clotrimazole and increasing this to 80 mg/kg/day in divided doses. Clotrimazole in these doses compared to ketoprofen at 50 mg. p.o. t.i.d. produced no significant differences in clinical measurements after eight weeks of treatment.
in 47 patients. One measurement, grip strength, favored clotrimazole at four weeks. There was a trend in favor of the clotrimazole group after four weeks and the consumption of analgesics was significantly lower in this group during the second month. It was felt in our study that we could reduce type II error by increasing sample size and that by increasing the duration of clotrimazole administration to 12 weeks and comparing it to placebo, a difference could be found if it existed.

There were statistically significant improvements in clinical measurements in both the placebo group and the clotrimazole group but the level of these changes were not statistically significant between the groups. The trend toward improvement in the clotrimazole group might have reached statistical significance had a larger number of patients been included in each group, larger doses of clotrimazole been employed or a longer treatment regimen been utilized.

Entry erythrocyte sedimentation rates were significantly higher in the clotrimazole group than the placebo group. However, when calculating the MRAI (13) in which the erythrocyte sedimentation rate is used in part, no difference could be detected in disease activity.

This study resulted in a greater occurrence of adverse experiences and withdrawals when using clotrimazole than was noted in previous studies (11,12). Differences in definition of adverse experiences and concomitant NSAID treatment could explain, in part, the comparatively large numbers of adverse experiences in our study. The predominance of upper gastrointestinal symptoms confirms Wotjulewski's experience (12). An explanation of the complaint of burning upon urination was not found when examining the urine chemistry and sediment.

In conclusion, this study revealed no significant difference in efficacy in patients treated for at least four weeks with either clotrimazole or placebo. Adverse experiences were significantly greater in the clotrimazole treated group. These findings thus do not support a therapeutic role for clotrimazole
as utilized in this study for the treatment of patients with rheumatoid arthritis.


Table 1. Changes in Clinical Measurements in Patients Completing 4-12 Weeks of Treatment with Clotrimazole or Placebo*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo (n=34)</th>
<th>Clotrimazole (n=30)</th>
<th>p+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Difference</td>
</tr>
<tr>
<td>Grip Strength (mm Hg)</td>
<td>120 ± 12.2</td>
<td>134 ± 12.7</td>
<td>+14.9 ± 5.4$</td>
</tr>
<tr>
<td>Joint Count (0-60)</td>
<td>30 ± 2.7</td>
<td>28 ± 3.1</td>
<td>-2.6 ± 2.5</td>
</tr>
<tr>
<td>Patient Assessment of Pain (0-10)</td>
<td>6 ± 0.3</td>
<td>6 ± 0.4</td>
<td>-0.2 ± 0.3</td>
</tr>
<tr>
<td>Observer Assessment of Pain (0-10)</td>
<td>5 ± 0.3</td>
<td>5 ± 0.4</td>
<td>-0.1 ± 0.3</td>
</tr>
<tr>
<td>ESR (mm/Hr)</td>
<td>35 ± 4.2</td>
<td>38 ± 4.5</td>
<td>+2.8 ± 3.4</td>
</tr>
<tr>
<td>RA Latex (tube dilutions)</td>
<td>6 ± 0.5</td>
<td>6 ± 0.4</td>
<td>+0.1 ± 0.2</td>
</tr>
<tr>
<td>MRAI†</td>
<td>97 ± 5.9</td>
<td>93 ± 6.9</td>
<td>-4.2 ± 4.3</td>
</tr>
</tbody>
</table>

*Values shown are mean ± SEM
+Clotrimazole treated group versus placebo treated group by two sample test
$\ p<0.025$
§p<0.05
†Modified rheumatoid activity index
Table 2. Summary of Patients Withdrawing Prior to Study Completion

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Clotrimazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Number withdrawing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 weeks*</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total Withdrawals</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Reason for Withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse experience</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Lack of effect</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Unrelated+</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

*Excluded from efficacy analysis
+Intercurrent illness; lost to follow-up
Table 3. Number of Patients With Adverse Experiences by Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (n=37)</th>
<th>(%)*</th>
<th>Clotrimazole (n=36)</th>
<th>(%)</th>
<th>P+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>9</td>
<td>(24.3)</td>
<td>5</td>
<td>(13.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>2</td>
<td>(5.4)</td>
<td>2</td>
<td>(5.6)</td>
<td>0.98</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>14</td>
<td>(37.8)</td>
<td>23</td>
<td>(63.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>(32.4)</td>
<td>11</td>
<td>(30.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6</td>
<td>(16.2)</td>
<td>13</td>
<td>(36.1)</td>
<td>0.053</td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>(10.8)</td>
<td>6</td>
<td>(16.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>5</td>
<td>(13.5)</td>
<td>13</td>
<td>(36.1)</td>
<td>0.025</td>
</tr>
<tr>
<td>Liver Function Tests (elevated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>2</td>
<td>(5.4)</td>
<td>3</td>
<td>(8.3)</td>
<td>0.67</td>
</tr>
<tr>
<td>Sustained</td>
<td>3</td>
<td>(8.1)</td>
<td>5</td>
<td>(13.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>Other‡</td>
<td>3</td>
<td>(8.1)</td>
<td>8</td>
<td>(22.2)</td>
<td>0.092</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentage of patients in each group with adverse experiences (table includes patients with more than one adverse experience, therefore total does not equal 100%)

+Chi square analysis

‡"Other" includes upper respiratory infection symptoms and transient epistaxis
CLOTRIMAZOLE (C) VERSUS PLACEBO (P) IN RHEUMATOID ARTHRITIS (RA).

William B. Dennison, Robert A. Turner, June A. Johnson, Bradley Wells.

Medical School of Medicine, Winston-Salem, NC 27103.

This is the first placebo controlled double-blind trial using the imidazole C in the treatment of RA. A sufficient number (64) of patients were enrolled to provide a power ≥0.80 (possibility of false negative result ≤20%) using observations from a previous study with immunomodulating agents at this institution. A total of 73 patients with active classical or definite RA were randomized and given either 20mg/kg/day 2 days per week of C or a matching P. Thirty patients in the C group and 34 patients in the P group completed at least 4 weeks of therapy. The C group showed significant (P < 0.05) improvements in grip strength (X±SEM=125±10.3mmHg vs 138±11.5), joint count (27±3.0 vs 24±3.0) and patient assessment of pain (6±0.4 vs 5±0.4) when comparing initial to final measurements. The P group also had a significant (P<0.025) response in grip strength (120±12.2 vs 134±12.7). There was no significant difference in the response of the C group vs. the P group. Drop-out analysis revealed 18 patients in the C group withdrawing prior to completion (9-adverse experiences, 5-lack of effect, 4-other, i.e. intercurrent illness, lost to follow-up, etc). In the P group, 11 patients withdrew (1-adverse experience, 5-lack of efficacy, 4-other). Total adverse experiences were more frequent in the C treated group (86) than in the P group (60) with a significant (P<0.05) increase in the occurrence of upper GI (23 vs. 14), GU (13 vs. 6) and CNS (13 vs. 5) symptoms. There was no difference in the occurrence of symptoms described as Herxheimer-like reactions. This study, using a placebo group and an adequate patient population as determined from previous studies, showed statistical evidence of toxicity but not efficacy for C in the treatment of RA.

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