Randomized Double Blind Trial of an Ayurvedic Plant Derived Formulation for Treatment of Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate RA-1, a standardized plant extract formulation, traditionally considered a safe, effective antiarthritic in the Asian-Indian Ayurvedic medicinal system.

Methods. One hundred eighty-two patients with active-on-chronic rheumatoid arthritis (RA) participated in a 16 week randomized, double blind, placebo controlled, parallel efficacy clinical drug trial in Pune, India. Tenderness, pain, swelling, and several other efficacy measures were assessed by (1) ACR core set 20% and 50% improvement; (2) ACR 20% improvement response. An intent-to-treat analysis was performed; $p < 0.05$ considered significant.

Results. Seventeen patients withdrew (active = 9; placebo = 8); none withdrew due to drug toxicity. An unprecedented placebo response (often $p < 0.001$ in within-group change) was observed. The active RA-1 group remained numerically superior at all evaluation timepoints. RA-1 demonstrated few significant differences: (1) increased proportion with 50% reduction in swollen joint count (95% CI ~1.52, 29.90) and swollen joint score (95% CI ~0.91, 28.73); (2) reduced rheumatoid factor (95% CI ~–303.7, –2.72); 39% in the RA-1 group versus 30% placebo showed ACR 20% improvement (95% CI ~–5.48, 24.59). Only minor side effects were seen, with no significant differences by treatment group.

Conclusion. In a trial with sufficient power, RA-1 revealed efficacy that was not significantly superior to the strong placebo response, except for improvement in joint swelling. Further, the effect on RF and good safety profile led to an open label phase. (J Rheumatol 2000;27:1365–72)

Key Indexing Terms:
RHEUMATOID ARTHRITIS AYURVEDA CLINICAL TRIAL

Plants remain an underexploited source of therapeutic drugs. Numerous medicinal plants indigenous to the Indian subcontinent have been used by Ayurvedic practitioners to treat all forms of arthritis since ancient times[1]. However, the formulations used are complex and difficult to standardize. From a modern scientific viewpoint, they require controlled clinical drug trials before they can be accepted universally.

A standardized formulation, called RA-1, was prepared from purified plant extracts of *Withania somnifera* (ashwagandha), *Boswellia serrata* (gugulla), *Zingiberis officinale* (adrak or ginger), and *Circuma longa* (haldi or circumin). Experimental animal studies[2-6] have documented the antiinflammatory, immunomodulatory, and antiarthritic effect of several Ayurvedic medicinal plants including the above. The formulation was constituted along the principles of Ayurveda and its safety was demonstrated in acute, subacute, and chronic toxicity studies in rats (Naik SR, Mazumdar AN, unpublished observations). Initially, qualitative identification of the known "markers" of purified plant extracts in RA-1 was performed by thin layer chromatography using a gel scanner. Subsequently, using Waters' (Vienna, Austria) high performance liquid chromatographic gradient, area-under-the curve was recorded for varying quantities of individual plant extract markers to obtain data for creating controls for large scale production of RA-1. After several cycles of HPLC analysis (ensuring reproducibility) and other physical tests, it was concluded that about 90% standardization of RA-1 had been achieved.

We compared the efficacy and toxicity of an orally administered RA-1 active preparation with that of a placebo in the treatment of patients with rheumatoid arthritis (RA).

MATERIALS AND METHODS

Phase 1 of the study consisted of a 16 week randomized double blind placebo controlled parallel efficacy clinical trial carried out at the Center for Rheumatic Diseases (CRD), Hermes Doctor House, Pune, India. The protocol was co-developed by Dr. R. Polisson, Clinical Director, the Arthritis Unit, Massachusetts General Hospital, Boston, USA, in consultation with the senior author (AC), and based on American College of Rheumatism (ACR) guidelines[7]. It was approved by the appropriate insti-

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tutional review board/ethics committee of the medical center. The randomized phase was to continue as an open label phase.

Selection criteria. Patients 18 years of age or older with RA of more than 6 months' duration and with disease onset after 16 years of age, with active disease, were eligible; ACR functional class IV were excluded[8]. All patients were to fulfill the ACR 1987 revised criteria for the disease classification[9]. Active disease[10] was defined by the presence of at least 3 of: (1) more than 5 painful-on-motion/tender joints; (2) > 2 swollen joints; (3) morning stiffness ≥ 45 min; and (4) Westergren erythrocyte sedimentation rate (ESR) ≥ 28 mm. A patient was considered eligible if a relapse of 2 months or more had ensued after cessation of all second line drugs (methotrexate, gold, penicillamine, corticosteroids) for 6 months; sulfasalazine or chloroquine for 2 months; Ayurvedic preparations for 1 month; or a failure (inefficacy or toxicity) of an adequate trial of a nonsteroidal antiinflammatory drug (NSAID). Daily fixed dose prednisolone, not exceeding 7.5 mg and stable for the month preceding enrollment, was permitted. Enrolled women were successfully using contraceptives or were menopausal.

Exclusions included pre-existing diseases/abnormalities involving the liver, kidneys, blood, or pancreas; history of malignancy; lactation or pregnancy; and any major illness or anticipated surgery compromising study participation.

Selection. Three hundred ninety patients (female:male 5.5:1), with clinical diagnosis of RA (AC) attended "diagnosis and therapy guidance arthritis camps" that were free of charge and were further examined for their eligibility to enroll in the drug trial. These one-day arthritis camps were part of a 3 month community based campaign in the Pune metropolis (population 1.6 million) to create public awareness on rheumatic diseases. The methodology of the camps has been published[11]; briefly, the schedule is well advertised and patients are requested to register by phone or in person. Twenty-six camps were conducted,usually over weekends, in an accessible private medical center. Camp attendance was restricted by the availability of preplanned medical resources on an individual day (larger numbers, up to 125, attended Sunday camps). A majority of patients did not register in advance and were seen on first-come, first-served basis. A total of 1422 patients (female:male 5:2) were evaluated. The first 182 patients (female:male 5:1) from the RA cohort who satisfied the above criteria enrolled and gave informed consent. The initial 6 weeks of the 8 week run-in period of the drug trial overlapped with the arthritis camps. Patients were entered on the recruitment day, in groups of 5 to 7 (identified serially by order of camp attendance and selection).

Patients were assigned to one of the 2 treatment groups [RA-1 active (89 patients) or placebo (93 patients)] by a computer generated randomization schedule. Patient demographics are shown in Table 1. A higher proportion of females than generally seen in our RA patients[12] were enrolled in both the treatment groups (female:male 5:1), but this was consistent with the preponderance of females observed in the camps and the RA cohort. A subset of 148 (81%) had moderate to severe (class II and class III) arthritis; 149 (82%) were seropositive for rheumatoid factor (RF). There were no significant imbalances between the treatment groups.

After enrollment, each patient was admitted to the medical center for 5–7 days. Although patients were asked to discontinue NSAID 3–5 days prior to entry, the initial 2 days (extended in doubtful cases) of admission ensured proper NSAID washout and provided an opportunity to educate patients on their trial medication and followup instructions; instructions were provided both orally and in writing. Baseline measures were recorded after the NSAID washout. Patient compliance was checked via surprise house visits and pill counting.

Evaluation criteria. Physician assessed measures included ARA functional class upon trial entry[7], and other core set measures of disease activity[6]. Criteria included (1) joint count and score for tenderness on pressure and/or pain on motion in 68 diarthrodial joints[6], on a scale of 0 = none, 1 = positive response on questioning, 2 = spontaneous response elicited, 3 = withdrawal by patient upon examination; (2) joint count (JCSW) and score

Table 1. Patient demographics at study entry.

Variable	Placebo (n = 93)	Active (n = 89)
Mean age (yrs)	45	45
Sex		
Female	80 (86)	72 (81)
Male	13 (14)	17 (19)
Family history (RA)	18 (20)	23 (25)
Mean disease duration (yrs)	8	6
Disease severity†		
Mild	15 (16)	19 (21)
Moderate	47 (51)	41 (46)
Severe	26 (28)	25 (28)
Very severe	5 (5)	4 (4)
Functional class		
I	0 (0)	0 (0)
II	56 (76)	50 (72)
III	18 (24)	19 (28)
Prednisolone use (5.3 mg/day)	36 (39)	40 (45)
Radiological erosions (hands)	64 (69)	62 (70)
RF positive	72 (81)	77 (83)
ESR > 60 mm/h	33 (37)	32 (34)

†Physician global assessment.
Values in parentheses are percentages.

(JSSW) for swelling of 66 joints, evaluated for bone contour loss severity from 0 (none) to 3 (bulging synovial proliferation); (3) grip strength when seated and compressing an adult blood pressure cuff bag with an outstretched unsupported arm, 3 readings summed for right and left side; (4) walking time in seconds for 50 feet unaided; and (5) physician global assessment (PHYG) of disease activity, on a 1 (asymptomatic) to 5 (very severe) ordinal scale.

Patient assessment included (1) duration of morning stiffness in minutes on the day before the visit; (2) severity of pain on a 100 mm vertical visual analog pain rating scale; (3) patient global assessment (PATG) of disease activity on a 1 (asymptomatic) to 5 (very severe) ordinal scale; and (4) functional assessment using a modified version of the Stanford Health Assessment Questionnaire (HAQ)[13], covering 8 major daily activities with a maximum total score of 24; modified HAQ (e.g., activities sitting cross-legged on floor, squatting, customary house chores/cooking and eating style, travel by bus and auto-rickshaw, etc.) designed for the Indian setting and appropriately validated[14].

Investigations. All laboratory and radiology work was carried out in an affiliated diagnostic center, which is laboratory standardized with the UK Wellcome group. RF and C-reactive protein (CRP) were quantitatively measured by nephelometric assays (Beckman ICS Instruments, Fullerton, CA, USA) and serum interleukin 6 (IL-6) measured by immunoenzyme assay (system components supplied by Medgenix, Fleurus, Belgium) in the Pune Centre. IL-6 values were also obtained by a cell based bioassay (sensitivity 0.1 unit) carried out in the Center for Rheumatic Diseases, Royal Infirmary, Glasgow, UK.

Blood chemistries, urinalysis, Westergren ESR, RF, CRP, and IL-6 were measured at baseline, Week 16 endpoint, or on patient withdrawal/termination from study. Routine laboratory data for efficacy and safety/toxicity were also generated during the followup visits of the trial. Nonsterile women were tested for pregnancy at baseline and 9 week and 16 week followup. Certain changes or abnormalities in blood or platelet count, or other serum or metabolic variables mandated patient withdrawal from the study.

Efficacy. The primary efficacy/improvement was defined as (1) 20% and 50% improvement response for individual core set variables[6]: reduction of

2 grades or from grade 2 to grade 1 in patient global and physician global assessment; and (2) an ACR 20% improvement response[15].

Although efficacy and safety evauations were carried out at 3, 6, 9, 12, and 16 week followup, the time point for evaluation of the primary efficacy improvement was the 16 week endpoint (with last observation carried forward). The additional efficacy analysis between time endpoints was carried out, but few important conclusions are presented due to increased likelihood of chance findings using a large number of comparisons and efficacy variables.

Data handling. Manual and computer checks for consistency and errors were performed on all data at the CRD, Pune; data were then transferred to Boston Biostatistics, USA, for the final decoding and statistical analysis; medication was decoded (PL) 4 weeks after conclusion of the randomization phase. Prior to decoding, signed copies of the case record forms and data were kept with the chief investigator, chief statistician, and the sponsors.

Drug administration. Prior to the trial's start, the manufacturer provided the estimated required quantities of RA-1 and identical placebo tablets, ensuring uniformity and standardization. Patients received RA-1 or identical placebo tablets, 2 tablets thrice daily (total daily dose of 444 mg extract) immediately after meals. In case of clinical worsening at any endpoint during the trial, the chief investigator (AC) could increase dosage to 2 tablets 4 times a day; 28 of 80 completers in the RA-1 group and 44 of 85 completers in the placebo group had dosage increases ($p < 0.05$, Fisher's exact chi-squared).

The active drug/placebo was appropriately blinded and dispensed to patients based on computer selected randomized codes A/B; a paramedical worker was specifically employed for this purpose only. Neither the doctors nor the medical assistants had access to these codes or the code borne by the tablets.

Glucocorticoids and disease modifying antirheumatic drugs (DMARD) were not permitted for one month prior to enrollment. Patients already taking prednisolone could continue their preenrollment regimen as described above. NSAID were not permitted during the study. Oral paracetamol was permitted as the rescue analgesic on prn basis and dispensed as tablets of 500 mg each; consumption was monitored.

Statistical design. This study was designed to detect a 20% difference in the proportion responding with 80% power and 5% Type 1 error according to a 2-sided test. The goal was to have at least 65 patients available per treatment group at conclusion, allowing for an expected 20% dropout rate. An intent-to-treat analysis was performed to assess efficacy for all patients randomized and enrolled into the study with baseline data. The level of significance was $p < 0.05$, 2-sided, and 95% confidence intervals (CI) were used to study the effect size. Patients who were terminated early for treatment related reasons were classified as nonresponders for the intent-to-treat analysis. A single sample t test was used to test within-group changes. The Mann-Whitney test evaluated continuous variables, while Fisher's exact tests were used to evaluate categorical outcomes including response. SAS (Version 6.08, Cary, NC, USA) and StatXact (Version 2.0, Cambridge, MA, USA) were used for analyses.

RESULTS

A total of 165 patients (90.6% of the original group; 80 active and 85 placebo) completed 16 weeks of double blind therapy. Seventeen patients (9 active, 8 placebo) withdrew/were terminated for reasons other than drug toxicity; this was only 9.3%, fewer than half the expected number. RA-1 and placebo patients were equally represented among the 5 withdrawals for therapy failure: 4 for followup failure, and 4 for unrelated concurrent health problems. Two RA-1 patients withdrew due to unacceptable concurrent (antipsychotic) medicines; 2 placebo patients withdrew due to adverse events.

The mean change in efficacy measures at the Week 16 endpoint by treatment group and the difference between the mean change over 16 weeks in the groups are shown in Tables 2 and 3; although improvement was numerically superior in the RA-1 group, it was not statistically significant. However, the RA-1 group showed significant improvement by Week 16 endpoint with respect to (1) an increase in the mean change ($p = 0.02$) and the median difference of change ($p = 0.003$) in the rise in hemoglobin, (2) reduction in the mean change ($p = 0.01$), and the median difference of change ($p = 0.011$) in the RF titer ($p = 0.01$).

Table 4 shows the proportion of patients with 20% improvement in individual efficacy variables and ACR 20% and 50% response in the treatment groups; once again, although the RA-1 group was superior, especially with impressive differences seen for joint counts for pain/tenderness and swelling and physician global assessment, none of the differences were statistically significant. An "ever" (anytime during the 16 week trial period) maximum of ACR 20% improvement response was seen in 44% of patients from the active group versus 33% from the placebo group ($p = 0.17$). Figure 1 presents the ACR 20% improvement response seen in the treatment groups at different evaluation time points in the trial.

Figure 2 presents the proportion of patients with 50% or greater improvement change in clinical efficacy measures

Table 2. Mean change in clinical efficacy variables (95% CI) from baseline to Week 16 endpoint: intent-to-treat analysis.

Variable	RA-1 (n = 89)		Placebo (n = 93)		Difference
	Baseline	Change	Baseline	Change	
Joint count pain	31.83 (28.30, 35.36)	–13.47 (–16.96, –9.97)	34.00 (30.53, 37.47)	–11.61 (–15.07, –8.15)	–1.86 (–6.74, 3.03)
Joint count swelling	15.85 (13.84, 17.87)	–9.13 (–11.12, –7.14)	16.78 (14.70, 18.87)	–8.20 (–10.09, –6.30)	–0.93 (–3.66, 1.80)
Pain (VAS)	5.90 (5.46, 6.35)	–1.37 (–1.90, –0.84)	5.99 (5.59, 6.40)	–1.18 (–1.72, –0.65)	–0.19 (–0.94, 0.56)
HAQ	12.77 (11.44, 14.10)	–3.72 (–5.23, –2.20)	12.37 (11.24, 13.49)	–2.67 (–3.87, –1.46)	–1.05 (–2.97, 0.87)
Patient global assessment	3.39 (3.20, 3.59)	–0.50 (–0.70, –0.30)	3.38 (3.20, 3.55)	–0.36 (–0.56, –0.16)	–0.14 (–0.43, 0.14)
Physician global assessment	3.11 (2.92, 3.29)	–0.86 (–1.05, –0.67)	3.23 (3.07, 3.39)	–0.74 (–0.95, –0.53)	–0.12 (–0.41, 0.16)

Table 3. Mean change in laboratory efficacy variables (95% CI) from baseline to Week 16 endpoint: intent-to-treat analysis.

Measure	RA-1 (n = 89)		Placebo (n = 93)		Difference
	Baseline	Change	Baseline	Change	
ESR	56.61 (49.86, 63.35)	+0.14 (–6.31, 6.59)	55.68 (48.95, 62.40)	+1.78 (–3.17, 6.73)	–1.64 (–9.71, 6.43)
Hb	11.85 (11.55, 12.14)	+0.77 (0.51, 1.03)	11.72 (11.39, 12.06)	+0.39 (0.13, 0.65)	0.38 (0.01, 0.74)
CRP	159.80 (98.88, 220.73)	+80.81 (12.12, 149.51)	188.11 (108.21, 268.02)	+65.31 (7.48, 123.14)	15.50 (–73.68, 104.69)
IL-6	155.22 (112.85, 197.58)	–54.42 (–98.26, –0.58)	132.51 (97.32, 167.69)	–57.77 (–115.25, –0.29)	3.35 (–67.94, 74.64)
RF	505.66 (335.76, 675.56)	–152.6 (–282.83, –22.36)	457.50 (350.90, 564.10)	0.61 (–74.80, 76.01)	–153.21 (–303.7, –2.72)

Table 4. Proporation of patients (%) with 20% improvement change in efficacy variables, 20% ACR and 50% ACR response, at Week 16 endpoint relative to baseline. 1 unit change considered significant for patients and physician global assessment.

Variable	RA-1 (n = 80)	Placebo (n = 85)	Difference 95% CI
Joint count pain, tenderness	70	57	–1.20, 26.54
Joint count swelling	83	73	–1.87, 21.93
Pain, VAS	53	46	–7.93, 21.07
HAQ	54	49	–10.04, 18.98
Patient global assessment	45	44	–14.70, 14.16
Physician global assessment	69	57	–3.7, 24.46
ESR	36	29	–7.73, 19.33
ACR 20	39	30	–5.48, 24.59
ACR 50	15	5	–1.11, 19.64

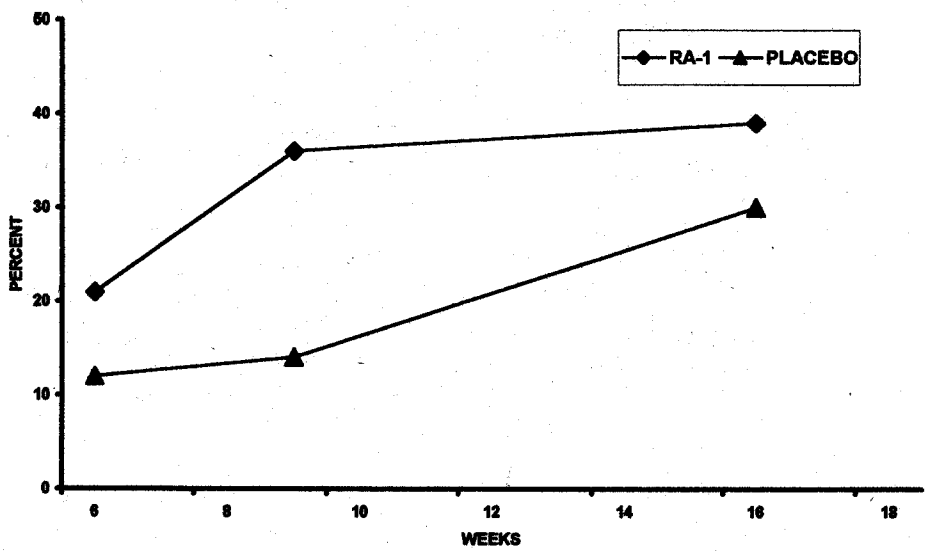

Figure 1. Proportion of patients showing ACR 20% improvement response by treatment group.

by treatment group; for both the joint count (95% CI 1.52, 29.90) and the joint score (95% CI 0.91, 28.73) for swelling, the improvement was significant ($p < 0.05$) in the RA-1 group. The active RA-1 group also showed significant improvement with respect to increased proportion of patients who "ever" showed a 50% or greater reduction in swollen joint count ($p = 0.03$) and swollen joint score ($p = 0.04$). The active group showed better response (but not significant) for the primary efficacy variables at all evaluation time points in the trial, with few significant observations, i.e., (1) at 9 weeks and 12 weeks followup a larger proportion showed > 50% reduction in ESR; (2) both patient

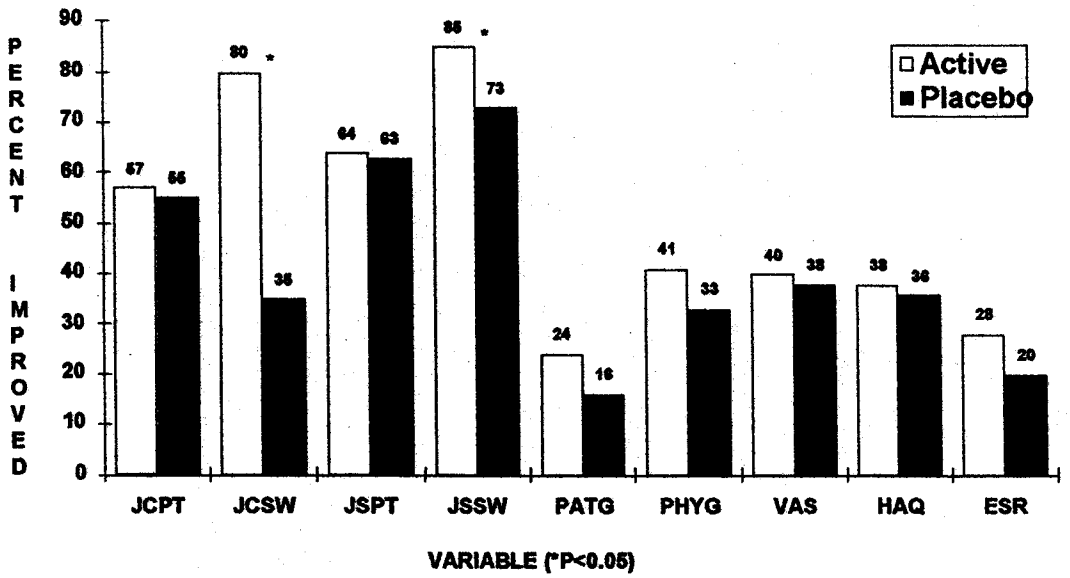

Figure 2. Fifty percent improvement during the randomization phase from baseline. JCPT: joint count for tenderness on pressure; JCSW: joint count for swelling; JSSW: joint score for swelling; PATG: patient global assessment for disease activity; PHYG: physician global assessment for disease activity; VAS: visual analog scale; ESR: erythrocyte sedimentation rate.

and physician global improvement rose more sharply between Weeks 12 and 16 (data not shown).

Despite an unexpected significant improvement in numerous clinical and laboratory efficacy measures in the placebo group (p often < 0.001) compared to the baseline, the active group remained numerically superior to the placebo group in all outcome efficacy measures; statistically significant improvement in the active group was achieved in the variables mentioned above.

As per the treatment records, although the quantity of paracetamol consumed was marginally higher (p > 0.05) in the placebo group, the data was considered inappropriate due to several flaws: although advised as prn use, numerous patients admitted having consumed 2 to 3 tablets daily in anticipation of pain, and further, often failed to return empty paracetamol tablet foils (in sharp contrast to empty foils from the intervention drug, which were returned diligently).

No patient achieved remission during the trial period[16]. Further, the subgroups of RF seropositive patients and patients not taking steroids showed similar results between the 2 treatment groups (data not shown).

No patient suffered from or withdrew because of a major side effect. Few patients experienced minor gastrointestinal upsets or headaches, lasting less than 5 days and responding to conventional therapy. There were no significant differences in the side effects profile between the active and the placebo groups (Table 5).

Table 5. Number of patients (%) with minor side effects/toxicity events, by treatment group. Values in parenthesis are percentages.

Side effects	Placebo (n = 93)	RA-1 (n = 89)
Anorexia	16 (17.2)	10 (11.2)
Nausea	13 (14)	12 (13.5)
Diarrhea	7 (7.5)	6 (6.7)
Constipation	9 (9.7)	7 (7.9)
Epigastric pain/burning, retrosternal burning	24 (26)	16 (18)
Vomiting	7 (7.5)	4 (4.5)
Loss of body weight	3 (3.2)	5 (5.6)
Pruritus generalized	19 (20.4)	18 (20.2)

DISCUSSION

Although Ayurvedic medicinal plant extracts, similar to RA-1, are used extensively in India as antiarthritic agents, clinical evidence to validate their efficacy is sparse. It is mandatory to add that Ayurveda advocates a holistic approach in treating disease and along with medicines (usually derived from plants and minerals), lifestyle modificatons and restrictions (usually of diet) are considered essential; ethnomedical validation at its best can only be focused on "medicines" because it would be near impossible to apply modern scientific means to the entire system. Few recent Indian trials[17,18] have tried to evaluate the therapeutic usefulness of Ayurvedic medicinal plants, but have been grossly limited in their design, controls, number of patients, and allowing concomitant use of NSAID.

The protocol of the current trial presumed that a 16 week blinded trial would suffice to detect any significant RA-1 toxicity, and that RA-1 would demonstrate a slow onset of clinically significant NSAID effect and some biological DMARD-like effect: hence the exclusion of concurrent

NSAID or DMARD use. As described above, some of the RA-1 ingredients have shown both antiinflammatory and immunomodulatory effects in experimental animal studies, especially with reference to *W. somnifera*[2-5] and *B. serrata*[6]. A small sample Asian Indian drug trial[17], using similar formulation, had concluded (see below) that besides providing symptomatic relief, the active intervention group had shown seroconversion of RF from positive to negative. Thus it was hypothesized that RA-1 is likely to demonstrate both NSAID and DMARD properties.

The 16 week duration chosen for this drug trial was guided by several factors: (1) a plant derived formulation would need sufficient time to clinically demonstrate analgesic, antiinflammatory, and disease modifying/immunomodulatory properties, if any; (2) advice obtained from Ayurvedic experts; (3) an Ayurvedic drug trial report[17]; and (4) ethical concerns.

Free or subsidized medical camps in India have been traditionally popular, in offering socioeconomically acceptable expert medical services, camps for cataract surgery and blood donation in particular. Although orthopedic camps, usually a mixture of surgical correction of deformities and therapy for arthritis, have been in vogue, camps solely dedicated to arthritis have been a recent phenomenon[11,19]. However, to our knowledge, they have never been used for enrolling patients into drug trials, as in this study. It is possible to make sensible speculations about the selection bias introduced by these camps affecting outcome. Camps can provide a wider choice of community sourced naive patients in a shorter period of time, resulting in saving in time and money; a better quality of "qualifiers" can be quickly enrolled. However, camps such as these need expert management, especially from the viewpoint of allaying community fears regarding drug trials. But the camps per se are also prone to many influences arising from sociopolitical and personal concerns (especially of their managers). It would be near impossible to apply sound randomization selection procedures to the patients attending these camps. It would be only after the selection of a large cohort that strict eligibilty criteria and a randomization schedule for enrollment could be applied (somewhat akin to a stratified sampling), as in the current trial. A dominantly lower socioeconomic population strata, with an intense desire to seek evaluation and relief free of charge, is usually seen in the camps. In a hand-to-mouth society with preferential care for men, women are probably more tempted to seek free "care" in such camps, as was evident in the selection process of this trial. Thus, although there are significant operative factors affecting selection and outcome in such camps, hopefully an appropriate trial protocol would confine them to acceptable limits. It is also likely that some of the strong "placebo response" (see below) we observed stemmed from the inherent selection bias and attributes of the camps. Although providing a more realistic situation, the "selection" through camps in view of the strong "placebo competition" might have made the going tough for the candidate drug. But the latter is no excuse for the performance of the candidate drug.

It is tempting to speculate on other factors that might have influenced the outcome, adversely or otherwise. The washout period (carried out prior to baseline, Week 0) did not appear to unduly influence the baseline efficacy measures (Table 1), which otherwise showed an impressive disease activity, without any significant differences in the treatment groups. Patients engaged in demanding house and often livelihood chores could have fallen prey to "quick result" therapeutic co-intervention, once in a while, from their family doctor, without the knowledge of the trial officials. That patients in the placebo group could have surreptitiously resorted to NSAID is a farfetched possibility to defend the placebo effect. But the desire to seek relief, along with the popular belief in the connotations of efficacy and safety of Ayurvedic therapy, must have pushed some patients hard to continue — the dropout rate of the trial was surprisingly low.

The difficulties and the ability to achieve statistical significance in the presence of a strong unexpected placebo response in otherwise well designed clinical drug trials have been discussed and reported[20]. Other possible explanations of the strong placebo response in the patients range from an "opportunity" for those of poor socioeconomic status to participate in what they perceive as a "caring" drug trial, to a belief in natural remedies and the culturally valued, pain bearing traits of a community deeply rooted in tradition. A longer study duration would be advised to minimize the "opportunity" effect and "caring" components.

Encouragement for further study derives from the numeric advantage for RA-1 versus placebo in almost all outcome efficiency measures, although RA-1 did not achieve statistically significant differences in the mean values of the "change" (baseline to study exit).

A significantly greater proportion of patients in the RA-1 group showed > 50% reduction in joint swelling, a measure that is considerably objective, especially in view of the absence of concurrent use of NSAID or DMARD. Although the statistically significant increase seen in blood hemoglobin is unlikely to be clinically significant in the broader context of improvement in RA, it is still noteworthy in a community that often suffers from poor nutritional status. The precise biological role of RF remains elusive[21,22]; the significant reduction of RF titer by RA-1 is probably an indication of the immunomodulatory effect.

Standardization is a major hurdle with multiple purified plant extract based formulations. Identification of biologically active markers, as distinct from the chemical markers (often solvent based) for identification/standardization, is an equally challenging task. Plant extract formulations such as RA-1 would be ethically acceptable for clinical drug trials,

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