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Long term effectiveness of RA-1, a standardized Ayurvedic medicine as a monotherapy and in combination with disease modifying anti-rheumatic drugs in the treatment of rheumatoid arthritis

Arvind Chopra*, Manjit Saluja, Toktam Kianifard, Deepa Chitre, Anuradha Venugopalan

Center for Rheumatic Diseases, Pune, India

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ABSTRACT

Background: Data on long term use of Ayurvedic drugs is sparse. They may prove useful if combined with modern medicine in certain clinical situations (integrative medicine). We present the results of a long term observational study of RA-1 (Ayurvedic drug) used in the treatment of rheumatoid arthritis (RA).
Materials and methods: On completion of a 16 week randomized controlled study, 165 consenting volunteer patients were enrolled into a three year open label phase (OLP) study. Patients were symptomatic with persistent active disease and naïve for disease modifying anti-rheumatic drugs (DMARD). 57 patients were on fixed low dose prednisone. Patients were examined every 10–14 weeks in a routine rheumatology practice using standard care norms. They continued RA-1 (Artrex ™, 2 tablets twice daily) throughout the study period and were generally advised to lead a healthy life style. Based on clinical judgment, rheumatologist added DMARD and/or steroids (modified if already in use) to patients with inadequate response; chloroquine and/or methotrexate commonly used. Treatment response was assessed using American College of Rheumatology (ACR) efficacy measures and ACR 20% improvement index standard update statistical software (SAS and SPSS) were used; significant at $p < 0.05$.
Results: 158, 130 and 122 patients respectively completed evaluations at 1, 2 and 3 year primary end point. The ACR 20 response (range 34–40%) remained stable over three years ($p = 0.33$). Patients improved optimum for several measures by one year ($p < 0.05$) and this was sustained. The use of steroids varied from 42 to 49% patients at yearly end points (mean daily dose 5 mg prednisone); correspondingly the use of DMARD varied from 20 to 34% patients. 40% patients on RA-1 did not require DMARD/steroids for control of disease. 77% patients reported adverse events, albeit mild and mostly gut related, and not causing withdrawal. Several study limitations (especially self-selection) were reduced by the high patient retention and consistency in drug use.
Conclusion: RA-1 is safe and effective in the long term management of symptomatic active chronic RA. DMARDs and/or steroids can be used judiciously along with RA-1 to treat difficult disease/flares. Further studies are required to evaluate RA-1 in early RA. This paves way for research and application of integrative therapeutic approach in clinical medicine.

1. Introduction

Ayurveda is an ancient medicinal system and is popularly practiced in India [1–3]. The holistic treatment approach combines herbomineral formulations and lifestyle changes. Ancient classic texts are important references. Though in use for centuries, effectiveness in the modern context needs validation [4,5]. Plant based formulations are difficult to standardize [6]. Several research publications have attempted to unearth scientific evidence of efficacy of Ayurveda derived drugs to treat arthritis [7–13]. Cochrane reviews include a protocol on validation of Ayurvedic drugs in the treatment of RA [14,15].

We reported the efficacy and safety of RA-1, a standardized Ayurvedic drug, in the treatment of active symptomatic RA in a 16 week randomized placebo controlled drug trial [7]. Patients were

* Corresponding author.
E-mail address: crdp@vsnl.net (A. Chopra).
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naïve for disease modifying anti-rheumatic drugs (DMARD). 40% patients were permitted to continued stable fixed daily low dose (< 7.5 mg daily) prednisone. This maiden landmark study drew attention towards the therapeutic potential of a standardized Ayurvedic medicine. Inspite of the improvement in the American College of Rheumatology (ACR), 20% response (primary efficacy) was not statistically significant and RA-1 performed better than the placebo in every efficacy variable with significant ($p < 0.05$) reduction in joint swelling and rheumatoid factor titer. Encouraged by the results, this study was undertaken as a three year open label phase (OLP) study.

Though doctors in India often combine Ayurvedic medicines and modern medicines in clinical practice, there is little scientific validation of this approach. It is prudent to add that to a large extent this kind of practice is surreptitious and unregulated. However, there is a growing enthusiasm for evidence-based integrative medicine [16] to treat difficult disorders such as RA.

In the current OLP, an integrative therapeutic strategy combining modern medicines and Ayurvedic drug (RA-1) was used to treat patients with inadequate response. The patient retention rate was more than 70% on study completion. We describe the effectiveness and safety of RA-1 in the treatment of RA in the current report.

2. Materials and methods

2.1. Site

The study was carried out at the Center for Rheumatic Diseases (CRD), Pune, in the Western India State of Maharashtra [17]. CRD is a community-based standard of care facility for rheumatic diseases.

2.2. Study design

This was a prospective observational study of three years following a protocol driven randomized study [7]. The OLP was guided by the overarching requirements of a true to life clinical practice. Patients were not segregated. Standard efficacy measures recommended by the ACR were used [18]. Patients were examined at 12–16 weeks intervals for efficacy and safety. All clinical services and RA-1 were provided free of cost to the patients. Patients were encouraged to continue RA-1 throughout the study period. Any worsening of symptoms and flares or persistent synovitis (inadequate response to RA-1) was managed by rheumatologists as per rheumatology practice norms. Rheumatologists added analgesics/NSAIDs (short term use), steroids and DMARD to a background RA-1 medication. All treatment decisions were made based on clinical judgment. The study design was approved by the CRD Ethics Committee.

2.3. Patient selection

165 consenting volunteer patients from the earlier randomized study were enrolled in the OLP [7]. Patients had active symptomatic disease and satisfied ACR classification criteria 1987 (randomization phase) (Table 1) [19].

2.4. Study and concomitant medication

RA-1 contained extracts of four medicinal plants- *Withania somnifera* (Ashwagandha), *Boswellia serrata* (Salai Guggul), *Zingiber officinale* (Shunti or ginger) *and Curcuma longa* (Haldi or circumin); Ayurvedic names shown in parenthesis. RA-1 was standardized and manufactured using modern pharmacological means [7]. Aqueous extracts were used for all plants except for guggul (aqua-alcoholic). The strength of plant extracts in each capsule of RA-1 was 90 mg Ashwagandha (root), 90 mg Shudh Salai Guggul (gum), 18 mg turmeric (rhizomes) and 24 mg ginger (rhizomes). In hindsight, we verify that the RA-1 formulation satisfied the CONSORT requirements (data not shown) [20]. Patients began with the optimum dose of RA-1 (investigational drug) which was 2 tablets (222 mg actives per tablet) twice daily following meals.

We followed current recommendations and our clinical practice norms while choosing modern medications and dosage schedule [21]. It was decided *a priori* to add steroids and/or DMARDs (oral chloroquine sulfate and/or methotrexate and/or sulfasalazine) to background RA-1 in patients with inadequate response or worsening of disease. Steroids were not to exceed 10 mg prednisone daily dose unless patient developed a systemic complication. We generally began with 5–10 mg prednisone daily and tapered to 2.5–5 mg daily once symptomatic improvement was sustained (6–8 weeks). We tried to stop steroids by a slow taper (1–2.5 mg every 2 weeks) if improvement was sustained for 6 months or so. Chloroquine sulfate was used in the dose of 250 mg daily. Oral methotrexate was begun at 10 mg single dose per week and was escalated up to 20 mg per week as per standard practice. The optimum dose of sulfasalazine was 2 gm daily in two divided doses. Patients continued concomitant drugs for coexisting diseases under supervision of their primary care physician.

In case of flare, patients were provided symptomatic relief with analgesics (paracetamol, tramadol) and/or NSAID (naprosyn, diclofenac, ibuprofen, nimesulide). The latter were used on *pro rata* basis or for short periods. NSAIDs were used sometimes round the clock for 4–8 weeks awaiting response from DMARD.

Patients were advised to maintain reasonable physical activity and fitness, reduce mental stress and consume healthy balanced diet. No specific advice was provided on any kind of diet or lifestyle changes.

2.5. Efficacy measures

In routine practice, all patients are recorded in a standard case record form which includes ACR core efficacy measures [18,22]. A 68 joint count was used to record pain/tenderness (JCPT) while 66 joints (hip excluded) were examined for swelling (JCSW). Both the physician and patients global assessment were recorded using a category scale (5 grades: asymptomatic = 1, mild = 2,

Table 1
Long term follow up study of patients suffering from rheumatoid arthritis (RA) and treated with RA-1 (standard Ayurvedic formulation): Baseline demographics.

Variable	Total (n = 182)
Mean age (yrs)	45
Sex (Female)	152 (83.5)
Family history (RA)	41 (22.5)
Mean disease duration (yrs)	7
Disease activity[a]	
Mild	31 (19)
Moderate	88 (48)
Severe	71 (28)
Very severe	9 (5)
Functional class (ACR)	
I	39 (22)
II	106 (58)
III	37 (20)
Prednisolone use (5.3 mg/day)	76 (42)
Radiological erosions (hands)	126 (69)
RF Seropositive	149 (82)
ESR >60 mm/h	65 (36)

[a] Based on Physician global assessment; n: total number of patients; ACR: American College of Rheumatology; RF: rheumatoid factor (nephlometry); Values in parentheses are percentages; see text for details.

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