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EXTRA MURAL RESEARCH

Immunological studies on Rheumatoid Arthritis treated with Homeopathic drugs: Results of the Pilot Study

Prakash Rao[1]* & Nagalakshmi Prasanna M[2]

[1]*Clinical Research Unit (Homoeopathy) Puducherry*
[2]*Senior Research Fellow, JIPMER, Puducherry*

Introduction & Objective: **Rheumatoid Arthritis (RA), a systemic disease, is characterized by a chronic inflammatory reaction in the synovium of joints. The inflammation is mediated by inflammatory cytokines. The objective of the study was to evaluate efficacy of homeopathic drugs and changes in the cytokine profile of rheumatoid arthritis patients treated with homeopathic drugs.**

Materials and Methods: **A total of 35 rheumatoid arthritis patients and 10 healthy controls completed this pilot study. The patients were treated with Rhus tox. (8), Pulsatilla (8) and Medorrhinum (9) according to totality of symptoms. The control group (10) received placebo. The patients were evaluated for disease activity at the time of enrollment in the study and after 3 weeks of therapy. Serum cytokine levels (IL-1α, IL-1β, IL-2, IL-6 and TNF-α) were measured at baseline and after 3 weeks of treatment.**

Result: **Patients receiving Rhus tox. showed significant improvement in Patient Visual Analogue Score (VAS) for global assessment of disease after 3 weeks of therapy compared to placebo group(p = 0.03). Patients receiving Pulsatilla showed a significant improvement in tender joint count (p = 0.01) at the end of 3 weeks compared to baseline. They also showed significant decrease in ESR (p = 0.02) as compared to placebo. However, hs-CRP values in treatment groups did not show significant difference when compared to the placebo group at baseline and after therapy. There was a significant decrease in IL 6 levels after 3 weeks of therapy in the patients treated with Rhus tox. and Medorrhinum compared to placebo (p=0.05 and 0.04 respectively). Surprisingly, there was a significant increase in IL 6 level in the placebo group compared to their baseline values (p = 0.04), suggesting ineffectiveness of placebo and worsening of the disease process.**

Conclusion: **In the present open label placebo controlled pilot study patients treated with 3 weeks of homeopathic drugs showed improvement in clinical features, reduction in parameters of inflammation and IL6 levels. These observations suggest a possible immunomodulatory role of homeopathic drugs in Rheumatoid Arthritis which need to be confirmed by further studies.**

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune/ inflammatory disease which leads to progressive joint damage and destruction[1]. The chronic inflammatory process is mediated through a complex cytokine network. The broad array of cytokines and factors produced in the affected joints, and the multiple cell interactions, dictate the evolution of arthritis[2]. Cytokines are protein messengers that convey information between and within cells via specific cell surface receptor molecules. The release of specific cytokines into the systemic circulation has been observed in a variety of inflammatory disease including RA[3]. Their concentration levels usually reflect disease severity and prognosis.

The cytokines are broadly divided into Pro inflammatory (IL-1α, IL-1β, IL-2, IL-3, IL-6, IL-7, IL-9, IL-8, IL-12, IL-15, IL-17, IL-18, IFNα, IFNα, IFNγ, GM-CSF, M-CSF, TNFα) Anti inflammatory (IL-4, IL-10, IL-11, IL-13, TGF-β) cytokines and Chemokines (IL-8,MIP-1α, MIP-1β, MCP-1, RANTES). In RA, the balance between pro-inflammatory and anti-inflammatory

* *Address for correspondence:*
Prakash Rao,
Clinical Research Unit (H)
1st Cross, Mangalakshmi Nagar
(Behind New Bus Stand),
Puducherry-605013

cytokines determines the degree and extent of inflammation, and thus can lead to different clinical effects. Anti-inflammatory cytokines or cytokine antagonists counteract the effects of pro-inflammatory cytokines and therefore the relative concentration of a cytokine to its inhibitor or antagonist determines its final effect[4,5].

In allopathic system of medicine Rheumatoid arthritis is treated by steroids, immunomodulators [Disease modifying anti rheumatic drugs (DMARDs)], immunosuppressive drugs and biological therapies[6].

In addition to being costly, these drugs have not been found to be effective in all patients with rheumatoid arthritis. They are also associated with many side effects, which sometimes can be life threatening. They can rarely be given for long periods in chronic autoimmune diseases like rheumatoid arthritis owing to financial constraints, toxic side effects and lack of sustained efficacy. Consequently, the patients feel helpless in the face of unpredictable, progressive, and disabling disease. These deficiencies of the allopathic medicines result in patients with the rheumatoid arthritis switching over to alternative treatment including homeopathy[7,8,9].

Therefore, there is an urgent need for new therapeutic agents with a high ratio of efficacy to toxicity including alternative systems of medicine for treating these disorders. ACR position paper on 'complementary and alternative medicine for rheumatic diseases' also supports integration of modalities proven to be safe and effective by scientifically rigorous clinical trials published in the biomedical peer review literature[10].

Due to lack of reported adverse effects of homeopathic medicines, they are extensively used for the management of various chronic disorders known to be miasmatic in nature. As the mechanism of action of homeopathic medications is not fully understood, it has not been possible to document their efficacy scientifically. However, with the advances in understanding the role of cytokines, Th-17 and T regulatory cells, immunopathogenesis of chronic autoimmune diseases is now understood better than before. Use of available advanced technologies to assess the effect of homeopathic drugs on these pathways may lead to understanding of the mechanism of action of these drugs.

The present pilot study has tried to look at the beneficial effect of homeopathic medicines on the immunological derangements in patients with rheumatoid arthritis by assessing changes in the profile of markers of inflammation (acute phase reactants) and inflammatory cytokines in the blood.

Materials and Methods

Subjects

Patients satisfying the American College of Rheumatology 1987 revised criteria for classification of Rheumatoid Arthritis, were recruited for the study[11]. They were treated with three homeopathic drugs (Rhus tox. (A), Pulsatilla (B), and Medorrhinum(C) according to homeopathic constitutional prescription. Each drug in its 30,200 & 1M potencies (single dose) at a gap of seven days were given in ascending order, followed by one week of placeto was the pattern of administration. In addition, each group had a matching control group receiving placebo. A total of 86 patients with RA were screened, of which 50 patients were enrolled under the study. Of the enrolled patients only 35 patients completed the study. Of these 35 patients, 8 subjects were treated with Rhus tox., 8 with Pulsatilla and 9 with Medorrhinum according to their constitution. Ten patients were treated with Placebo. Ten healthy, unrelated age and sex matched individuals were also recruited as controls for this study to assess normal cytokine levels in the population. Informed consent was obtained from both patients and controls before enrollment in the study. The study was cleared by the Institute ethics committee.

Three different weekly doses of Homeopathic drugs were administered to the patients:

S. No.	Name of the drug	Week 1	Week 2	Week 3
1	Rhus tox.	A1-30C	A2-200C	A3-1M
2	Pulsatilla	B1-30C	B2-200C	B3-1M
3	Medorrhinum	C1-30C	C2-200C	C3-1M
4	Placebo	D1-30C	D2-200C	D3-1M

The duration of treatment was three weeks (Baseline, 1st week (30 C), 2nd week (200C) and 3rd week (1M). The blood sample was collected at baseline and the end of 3rd week. Clinical data of patients were collected and RA disease activity was assessed at baseline and at the end of 3 weeks using DAS 28 score, a validated and widely used measure of disease activity.

Collection of Samples

Five ml of coagulated and 5ml of anticoagulated blood samples were collected from each patient in sterile bottles. Plasma was separated within 30 minutes of collection and stored at -80^0 Celsius for future estimation of cytokine levels.

Determination of Cytokine levels

The serum obtained from RA patients and healthy controls were analysed for IL-1α, IL-1β, IL-2, IL-6 and TNF-α using commercially available Human Cytokine ELISA kits following the manufacturers' instructions (Immunotech, France). Cytokine concentration was calculated from a standard curve of the corresponding human cytokine.

Determination of Laboratory parameters of Inflammation

The blood samples obtained from RA and healthy controls were used to determine ESR and High Sensitivity C-Reactive protein (hs-CRP) at the baseline and at the end of three weeks of treatment.

Statistical Analysis

The statistical data was obtained using software Graphpad InStat3. The results were expressed as mean ± SD and were used to determine the significance of differences; a value of $P < 0.05$ was considered statistically significant.

Results

Eighty six patients with RA (81 females and 5 males) were initially screened for enrolment in the study. Fifty four patients (52 females and two males) were found to have active disease and 35 in remission. The patients with active disease were enrolled in the study. Of the 54 enrolled patients only 35 completed the study (8 in Rhus tox. group, 8 in Pulsatilla, 9 in Medorrhinum, and 10 in Placebo). Their mean age was 45 years (range, 35-55 years), with a mean duration of disease less than one year. The healthy controls had a mean age of 38 years (range, 20- 52). The main reason for discontinuation was inability of the patient to report for follow up (12) followed by lack of efficacy of the treatment (7). Baseline characteristics of the patients are given in table 1.

Patients receiving Rhus tox. (group A) showed significant improvement in patient Visual Analogue Score (VAS) for global assessment of disease at the end of 3 weeks compared to placebo group ($p = 0.03$). The difference was not significant at the baseline. Patients receiving Pulsatilla (group B) showed a significant improvement in tender joint count ($p = 0.01$) **(Fig 1).** Patients receiving placebo (group D) showed markedly significant worsening in physician assessed Visual Analogue Score (VAS) for global assessment of disease at the end of 3 weeks compared to baseline ($p = 0.03$) **(Fig 2).** However, DAS 28 score (a composite score of disease activity consisting of swollen joint count, tender joint count, Patient Visual analogue score for global assessment of disease activity and ESR) did not change significantly after 3 weeks of treatment, although, there was a trend towards improvement. In addition, there was no significant difference in the DAS scores of patients treated with placebo and homeopathic drugs, though, patients treated with placebo showed deterioration in their disease activity evidenced by increase in their DAS score. **(Table 2)**

Table 1: Baseline Patient Characteristics

S. No.		Clinical Parameter			
		Rhus tox. (A) (n = 8)	Pulsatilla (B) (n = 8)	Medorrhinum (C) (n = 9)	Placebo (D) (n=10)
1.	Sex Males Females	 0 (0%) 8 (100%)	 0 (0%) 8 (100%)	 1 (11%) 8 (89%)	 0 (0%) 10 (100%)
2.	Age (yrs)	40.5 ± 13	36.5 ± 5.52	41.7 ± 12.54	40.1 ± 10.03
3.	Disease duration (months)	6 ± 4	7 ± 5	10± 6	8 ± 6
4.	Swollen joint count (28)	2.2 ± 1.9	2 ± 1.7	3.44 ± 3.1	2.6 ± 2.6
5.	Tender joint count (28)	5.7 ± 3.6	6 ± 5.8	7.2 ± 4.1	6.6 ± 5.0
6.	Early Morning Stiffness (min)	63.7 ± 73.7	54.37 ± 41.	118.3 ± 123.3	46.5 ± 41.3
7.	Patient VAS pain (0-10)	5.2 ± 0.7	5.62± 0.9	5.5 ± 1.2	5.4 ± 1.2
8.	Patient VAS (global) (0-10)	5.2 ± 0.7	5.6 ± 0.91	5.5 ± 1.23	8.7 ± 0.1
9.	Physician VAS (0-10)	5.1 ± 0.6	5 ± 0.9	5.4 ± 1.1	5.3 ± 1.1
10.	DAS 28 score	4.1 ± 1.12	4.08 ± 1.41	4.6 ± 0.77	4.27 ± 0.99

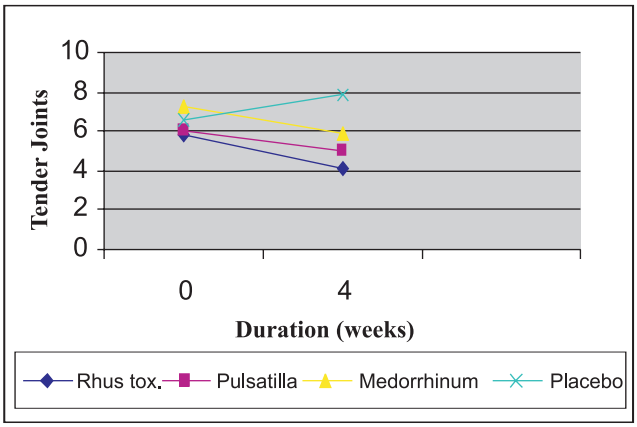

Figure 1: Tender joint count in RA patients treated with homeopathic drugs and placebo

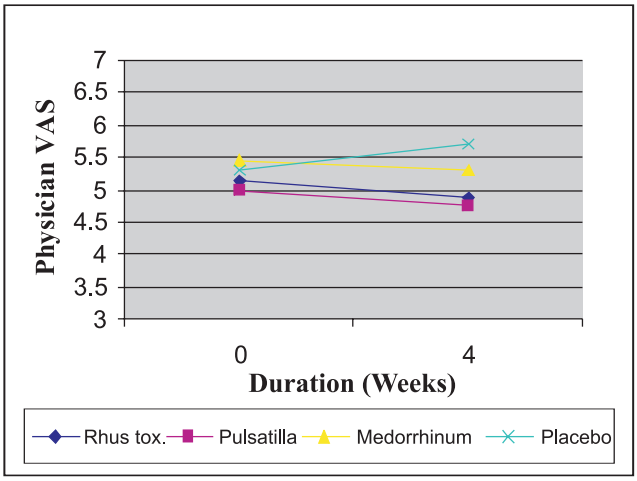

Figure 2: Physician VAS changes in RA patients treated with homeopathic drugs and placebo

Table 2: Changes in clinical parameters following treatment with Homeopathic drugs

* = significant ($p < 0.05$), NS = not significant

S. No.	Clinical Parameter	Week of Therapy	Drug						
			Rhus tox. (A)	P value (AD)	Pulsatilla (B)	P value (BD)	Medorr-hinum (C)	P value (CD)	Placebo (D)
1.	Swollen Joint	0 4 P value	2.2 ± 1.9 1.3 ± 1.5 0.06	NS NS	2 ± 1.7 1.8 ± 2.1 NS	NS NS	3.4 ± 2.4 3.44 ± 3.1 NS	NS NS	2.6 ± 2.6 3.7 ± 2.5 NS
2.	Tender joint	0 4 P value	5.7 ± 3.6 4.1 ± 2.5 NS	NS 0.07	6 ± 5.8 5 ± 5.3 0.01*	NS NS	7.2 ± 4.1 5.8 ± 4.5 0.07	NS NS	6.6 ± 5.0 7.8 ± 5.2 NS
3.	EMS	0 4 P value	63.7 ± 73.7 55.6 ± 60.8 NS	NS NS	54.3 ± 41.6 56.8 ± 60.2 NS	NS NS	118.3 ± 123.3 105 ± 106.6 NS	NS NS	46.5 ± 41.3 65 ± 50.8 NS
4.	Pt. VAS (pain)	0 4 P value	5.2 ± 0.7 4.8 ± 0.9 NS	NS 0.07	5.62 ± 0.9 5 ± 1.3 NS	NS NS	5.55 ± 1.2 5.4 ± 1.3 NS	NS NS	5.4 ± 1.2 5.8 ± 1.0 NS
5.	Pt. VAS (global)	0 4 P value	5.2 ± 0.7 4.8 ± 0.9 NS	NS 0.03*	5.6 ± 0.9 4.8 ± 1.3 0.07	NS 0.07	5.5 ± 1.2 5.5 ± 1.2 NP	NS NS	8.7 ± 0.0 6 ± 1.0 NS
6.	Physician VAS	0 4 P value	5.1 ± 0.6 4.8 ± 0.8 NS	NS NS	5 ± 0.9 4.75 ± 1.0 NS	NS 0.07	5.4 ± 1.1 5.33 ± 1.2 NS	NS NS	5.3 ± 1.1 5.7 ± 1.0 0.03*
7.	DAS (28)	0 4 P value	4.16 + 1.12 3.89 + 0.78 NS	NS NS	4.08 + 1.41 3.75 + 1.18 NS	NS NS	4.6 + 0.77 4.36 + 1.17 NS	NS NS	4..27 + 0.99 4.66 + 1.18 NS

Patients receiving Pulsatilla (group B) showed a significant decrease in ESR (p = 0.02) at the end of 3 weeks compared to placebo. The difference was not significant at the baseline. However, hs-CRP values in homeopathy treatment groups (A, B and C) did not show significant changes compared to Placebo group at baseline and after 3 weeks of therapy. Patients receiving Pulsatilla (group B) showed a significant decrease in ESR (p = 0.02) compared to placebo. The difference was not significant at the baseline. However, hs-CRP values in homeopathy treatment groups (A, B and C) did not show significant changes compared to Placebo group at baseline and after 4 weeks of therapy **(Table 3)**

There was a significant decrease in IL 6 level after 3 weeks of therapy in Rhus tox. (group A) and Medorrhoneum (group C) groups compared to Placebo (group D) (p = 0.05 and 0.04 respectively) **(Fig 3)**. The baseline values were not significantly different in both the groups. Thus, there was a downward modulation of IL 6 levels by Rhus tox. and Medorrhoneum. However, there was a significant increase in IL 6 level after 3 weeks of therapy in the placebo (group D) group compared to baseline values (p = 0.04) suggesting ineffectiveness of Placebo and worsening of the disease process **(Table 4)**. However, there was no significant change in TNF á values before and after treatment in both placebo and homeopathy treated patients.

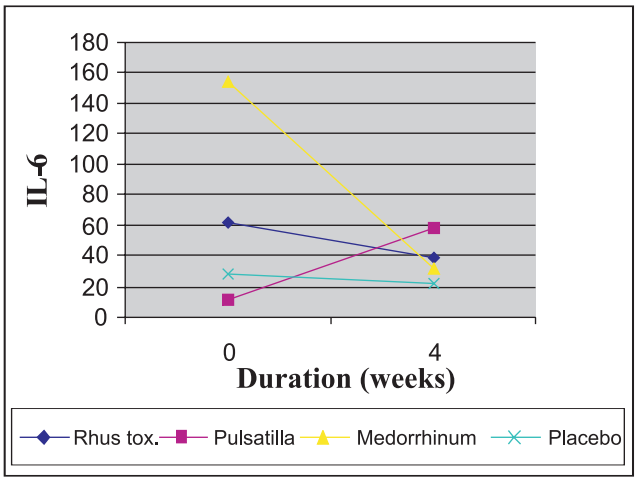

Figure 3: IL-6 response in RA patients treated with homeopathic drugs and placebo

Discussion

Rheumatoid arthritis (RA) is a systemic autoimmune disease localized preferentially in the synovial joints, resulting in joint destruction and permanent disability[1]. There is growing evidence suggesting that proinflammatory cytokines such as Tumour Necrosis Factor alpha (TNF-alpha), interleukin-1 (IL-1), interferon gamma (IFN-gamma) and interleukin-6 (IL-6), play an important role in the pathogenesis of this disease[2,12]. These inflammatory cytokines are present in the rheumatoid synovial membrane and participate in cell proliferation as well as in the synthesis of prostaglandins, metalloproteinases and other cytokines[3,4,5].

Patients with Rheumatoid arthritis often take alternative treatments[13], including homeopathy[14]. Gibson et al found a significant improvement in subjective pain, articular index, stiffness and grip strength in those patients receiving homoeopathic remedies whereas no change was noted in the patients who received placebo[15].

Table 3: Changes in Inflammatory parameters following treatment with Homeopathic drugs

S. No.	Laboratory parameter	Week of Therapy	Drug						
			Rhus tox. (A)	P value (AD)	Pulsatilla (B)	P value (BD)	Medorr-hinum (C)	P value (CD)	Placebo (D)
1.	ESR	0	41.25±20.31	NS	47±33.1	NS	46.8±21.24	NS	44.6±31.2
		4	20.31±23.9	NS	30±12.7	0.02*	47.37±26.59	NS	54.1±26.4
		P value	NS		NS		NS		NS
2.	CRP*	0	14.93±18.77	NS	15.2±10.6	NS	28.78±33.86	NS	
		4	15.8±24.1	NS	25.1±41.4	NS	50.66±55.1	NS	
		P value	NS		NS		NS		NS

* = significant (p < 0.05), NS = not significant

Table 4: Changes in cytokine profile following treatment with Homeopathic drugs

* = significant (p < 0.05), NS = not significant

S. No.	Cytokines	Week of Therapy	Rhus tox. (A)	P value (AD)	Pulsatilla (B)	P value (BD)	Medorr-hinum (C)	P value (CD)	Placebo (D)
1.	IL-1 alpha	0	3.2 ± 9.1	NS	25.0 ± 70.7	NS	11.4 ± 16.4	NS	22.1 ± 37.6
		4	6.7 ± 19.0	NS	23.7 ± 55.8	NS	11.5 ± 11.2	NS	27.3 ± 46.7
		P value	NS		NS		NS		NS
2.	IL-1 beta	0	2.4 ± 3.9	NS	2.6 ± 6.9	NS	154.4 ± 321.1	NS	0.4 ± 0.7
		4	3.9 ± 6.3	NS	3.82 ± 9.7	NS	52.3 ± 67.3	NS	12.5 ± 21.3
		P value	NS		NS		NS		NS
3.	IL-2	0	0	NS	0	NS	52.3 ± 67.3	NS	0.01 ± 0.01
		4	0	NS	0	NS	0	NS	0.3 ± 1.1
		P value	NP		NP		NS		NS
4.	IL-6	0	61.5 ± 74.2	NS	11.4 ± 254.9	NS	154.4 ± 31.4	NS	28.4 ± 20.7
		4	38.6 ± 27.6	0.05	58.2 ± 62.7	NS	32.14 ± 39.0	0.04*	21.4 ± 24.7
		P value	NS		NS		NS		0.04*
5.	TNF alpha	0	8.3 ± 4.2	NS	24.3 ± 11.98	NS	28.7 ± 14.9	NS	28 ± 17.2
		4	6.1 ± 4.0	NS	22.11 ± 7.3	NS	24.9 ± 12.9	NS	30 ± 22.5
		P value	NS		NS		NS		NS

In the present study, patients with Rheumatoid Arthritis received homeopathic drugs Rhus tox. (30C, 200C, 1M), Pulsatilla (30C, 200C, 1M), Medorrhinum (30C, 200C, 1M) and the control group was given placebo. Patients receiving Rhus tox. (group A) showed a significant improvement in Patient Visual Analogue Score (Patient VAS) for global assessment of disease at the end of 3 weeks compared to placebo group (p = 0.03). The difference was not significant at the baseline. Patients receiving Pulsatilla (group B) showed a significant improvement only in tender joint count (p = 0.01). There was no significant improvement in other clinical parameters of disease activity. There was no significant change in clinical parameters in patients treated with Medorrhinum (group C). Patients receiving placebo (group D) showed worsening in Physician assessed Visual Analogue Score (physician VAS) for global assessment of disease (p = 0.03). Patients receiving Pulsatilla showed a significant decrease in ESR (p = 0.02). However, hs-CRP values in treatment group did not show any significant change.

Recently, Sivalingam et al demonstrated the cytokine profiles in RA patients with active and inactive joint disease in a cohorot of Chinese rheumatoid arthritis (RA) patients[16]. The pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-18 and TNF-á) were significantly elevated in patients with RA, while TGF-â, an immunomodulatory cytokine, was elevated in control individuals. When these patients were categorized as active or inactive based on DAS scores, similar cytokines profiles were observed in both disease sub-groups. However, sTNF-R1 and sTNFR-2 were noted to be significantly elevated in inactive RA when compared to active disease. It appears that production of cytokine inhibitors may be associated with diminished disease activity. Similar phenomena can explain absence of any change in TNF alpha levels despite clinical response, in the treatment group in our study.

Conforti and Lussignoli have observed reduction in IL6 levels in rat paw edema model of inflammation[17,18]. Al Santo et al have shown Rhus tox. reduces Caraagreenan induced rat paw edema[19]. To the best of our knowledge, there is no literature on cytokine profile in Rheumatoid arthritis patients treated with homeopathic drugs. In the present study, a significant decrease was found in IL 6 level at the end

of 3 weeks of therapy in Rhus tox. and Medorrhinum groups compared to placebo (p = 0.05 and 0.04 respectively). The baseline values were not significantly different in both the groups. These observations suggest downward modulation of IL 6 levels by Rhus tox. and Medorrhinum. However, there was a significant increase in IL 6 level at the end of 3 weeks of therapy in placebo group, compared to baseline values (p = 0.04) suggesting worsening of the disease process due to ineffectiveness of Placebo.

There is conflicting data regarding the effectiveness of homeopathic drugs in rheumatoid arthritis. Andrade et al analyzed 44 patients with active Rheumatoid Arthritis treated with homeopathic drugs in a 6-month double-blind placebo controlled trial[20]. No statistically significant difference was found between both the treatment groups. It was concluded that the response to homeopathic drugs could be due to placebo effect. Gibson et al reported the results of a pilot study in which 41 patients with rheumatoid arthritis were treated with high doses of salicylate and the results were compared with 54 similar patients treated with homoeopathic drugs[21]. The patients who received homoeopathic drugs showed better response than those who received salicylate.

At present it is still not clear whether the homeopathic drugs are 'ineffective[22], the observed clinical effects are 'placebo response'[23] or genuine clinical effects[24]. In the present open label placebo controlled pilot study homeopathic treatment was found to be effective in some patients with rheumatoid arthritis and changes were noticed in a few inflammatory parameters. No side effects were reported in patients treated with homeopathic drugs. However, the significance of the results of this pilot study cannot be judged at present due to a small sample size and measurement of only a few inflammatory cytokines.

The initial trend shown by the present pilot study suggests that some homeopathic drugs may be superior to placebo in the treatment of Rheumatoid Arthritis. Of the measured cytokines, we found that IL6 was reduced following treatment, suggesting an immunomodulatory effect. Homeopathic drugs may work by reducing pro-inflammatory and increasing anti-inflammatory cytokines. In addition, the neuroimmune axis and T regulatory cells may also contribute to their clinical effect. Confirmation of the immunomodulatory properties of the homeopathic drugs requires measurement of a large number of pro and anti-inflammatory cytokines, Th17 and Treg responses in a large sample size of the patients. It should further be confirmed by in-vitro proliferation and cytokine expression studies to delineate the underlying molecular mechanisms.

References

1. We yand CM, Goronzy JJ. Pathogenesis of rheumatoid arthritis . *Med Clin N Amer* 1997; 81: 29–55.
2. Koch AE, Kunke l SL, Striate r RM. Cytokines in rheumatoid arthritis. *J Invest Med* 1995; 43:28–38.
3. Brennan FM, Maini N, Feldmann M. Cytokine expression in chronic inflammatory disease. *Br Med Bull* 1995; 51: 368–384.
4. Holt I, Coope r RG, Denton J, Me age r A, Hopkins SJ. Cytokine inter relationships and their association with disease activity in arthritis. *Br J Rheumatol* 1992; 31: 725–733.
5. Ronne lid J, Berg L, Rogberg S, Nilsson A, Albertsson K, Klareskog L.Production of T-cell cytokines at the single - cell level in patients with inflammatory arthritides: enhanced activity in synovial fluid compared to blood. *Br J Rheumatol* 1998; 37: 7–14.
6. Kenneth G. Saag, Gim Gee Teng, Nivedita M. Patkar, Jeremy Anuntiyo, Catherine Finney, Jeffrey R. Curtis et al. American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. Arthritis & Rheumatism (Arthritis Care & Research) Vol. 59, No. 6, June 15, 2008, pp 762–784.
7. Struthers G, Scott DL, Scott DGI. The use of 'Alternative treatments' by patients with Rheumatoid Arthritis. Rheumatol Int 1983; 3:151-2.
8. Panush RS, editor. Complementary and alternative therapies for rheumatic diseases. Rheum Dis Clin North Am 2000;26:i-xx1-197.
9. Institute of Medicine 2005: complementary and alternative medicine in the United States. Washington, DC: National Academies Press; 2005.
10. ACR position paper on 'complementary and alternative medicine for rheumatic diseases' presented by 'committee on rheumatological care' for distribution to ACR Members, Medical Societies, Allied Health Professional Societies, Arthritis Patients and National Center for Complementary and Alternative Medicine – NIH. August 2008.
11. Arnett FC, Edworthy SM, Bloch DA, Bloch DA, McShane DJ, Fries JF, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315-24.
12. Robak T, Gladalska A, Stepien M. Tumour necros is factor (TNF) family of receptors ligands in the se rum of patients with rheumatoid arthritis. *Eur Cytokine Netw* 1998; 9: 145–154.
13. Struthers G, Scott DL, Scott DGI. The use of 'Alternative treatments' by patients with Rheumatoid Arthritis. Rheumatol Int 1983; 3:151-2.
14. Jones WB, Linde K, Rameiz G. Homeopathy and Rheumatic disease. Rheu Dis clin North Am 2000;26:117-23.
15. Gibson R.G, Sheila L, Gibson M, MacNEILL A.D and Watson W Buchanan. Homoeopathic therapy in Rheumatoid Arthritis: evaluation by double-blind clinical therapeutic trial Br. J. clin. Pharmac. (1980), 9, 453-459
16. Sivalingam Suppiah Paramalingam, Julian Thumboo, Sheila Vasoo, Szu Tien Thio,Connie Tse,Kok-Yong Fong. In vivo Pro- and Anti-inflammatory Cytokines in Normal

and Patients with Rheumatoid Arthritis. Ann Acad Med Singapore 2007;36:96-9
17. Conforti A, Bertani S, Metelmann H, Chirumbolo S, Lussignoli S, Bellavite P. Experimental studies on the anti-inflammatory activities of a Homeopathic preparation. Biomed Ther 1997;15: 28-31) 64, 66)
18. Lussignoli S, Bertani S, Metelmann H, Bellavite P, Conforti A. Effect of Traumeel S. a homeopathic formulation, on blood-inducged inflammation in rats. Complement Ther Med 1999; 7:225-30)
19. Al dos Santo, FF perazzo, LGV Cardosso, JCT Carvallho. In vivo study of the anti-inflammatory effect of Rhus toxicodendron. Homeopathy 2007;96: 95-101).
20. Andrade LE, Ferraz MB, Atra E, Castro A, Silva MS. A randomized controlled trial to evaluate the effectiveness of homeopathy in rheumatoid arthritis. Scand J Rheumatol, 1991, 20:3, 204-8.
21. Gibson RG; Gibson SL; MacNeill AD; Gray GH; Dick WC; Buchanan WW Salicylates and homoeopathy in rheumatoid arthritis: preliminary observations. Br J Clin Pharmacol, 1978 Nov, 6:5, 391-5.
22. P Fisher, DL Scott. A randomized controlled trial of homeopathy in rheumatoid arthritis. Rheumatology 2001;40:1052-55
23. Aijiing Shang, Karin Huwiler- Muntener, Linda Nartey, Peter Juni, Stephan Dorig, Jonathan AC Sterne, Daniel Pewsner, Mathias Egger. Are the clinical effects of Homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. Lancet 2005; 366: 726-32.
24. RG Gibson, Sheila L M Gibson, A D MacNeill, W Watson. Homeopathic therapy in Rheumatoid arthritis : evaluation by double blind clinical therapeutic trial. Br J Pharmac 1980;9:453-9.