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# Complementary and Alternative Medicine in the Treatment of Rheumatoid Arthritis

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## 1. Introduction

Treatment of rheumatoid arthritis, a systemic, diverse and dynamic disorder, has made major progress over the past few decades. Early active treatment with disease-modifying anti-rheumatic drugs and biological agents can be highly beneficial for controlling inflammatory activity and preventing disability in many patients. However, the most effective new drugs are expensive and many patients with rheumatoid arthritis continue to have significant pain, restricted mobility, reduced muscle strength and low endurance. In addition, it is increasingly recognized that co-morbid conditions play a pivotal role in rheumatoid arthritis outcomes. For example, cardiovascular complications are the leading contributor to mortality in rheumatoid arthritis, accounting for approximately one half of all deaths. Osteoporosis, resulting in bone fractures, also represents a major source of morbidity in rheumatoid arthritis. Complementary and alternative medicine treatment and lifestyle behavioral modification may play a role in preventing rheumatoid arthritis-associated comorbidities and their complications.

Rheumatoid arthritis is characterized by synovial inflammation that leads to joint destruction, resulting in substantial long-term disability and a significantly shorter life expectancy. Many patients with rheumatoid arthritis experience high levels of pain, functional impairment, psychological distress and negative emotions, but these symptoms have limited pharmacological therapeutic options. Given the complexity of the therapeutic armamentarium used in rheumatoid arthritis, non-pharmacological therapies are increasingly attractive to those with chronic rheumatic pain conditions. Recently, complementary and alternative medicine therapies for arthritis have been heavily advertised and increasing numbers of chronic pain patients report utilizing alternative therapies. At the same time, clinical trials and observational studies have provided encouraging evidence that Acupuncture, Mind-body Therapy, Chinese herbs and Tibetan Medicine have some benefits for patients with rheumatoid arthritis. Indeed, integrative approaches combine the best of conventional medicine and the wisdom of complementary and alternative medicine. Thus, this chapter synthesizes the current body of knowledge on the therapeutic benefits of several types of Complementary and Alternative Medicine on pain and symptom relief in patients with rheumatoid arthritis to better inform clinical decision-making for our patients.

## 2. Acupuncture for rheumatoid arthritis

### 2.1 Acupuncture therapeutics

Acupuncture, originating in China more than 3,000 years ago, is one of the most popular sensory stimulation therapies. It is an ancient technique of inserting and manipulating fine needles to stimulate specific anatomic points, also known as acupuncture points or meridian points. There have been extensive investigations into the biological mechanisms of acupuncture (Cho et al., 1998; Darras et al., 1992; Dhond et al., 2008; Gao et al., 1997; Han & Terenius, 1982; Han, 1997; Harris et al., 2009; Hui et al., 2000; Hui et al., 2005; Kaptchuk, 2002; Kovacs et al., 1992; Langevin et al., 2001a; Langevin et al., 2001b; Langevin et al., 2007; Li et al., 2007; Napadow et al., 2005; Napadow et al., 2007; Napadow et al., 2008; Pariente et al., 2005; Wu et al., 1999; Zhang et al., 2005). Some of the best evidence is in relation to treatment of pain. Three previous systematic reviews examined the efficacy of acupuncture in patients with rheumatoid arthritis and reported that acupuncture has conflicting evidence for treatment of RA in the placebo-controlled trials (Casimiro et al., 2005; Lee et al., 2008; Wang et al., 2008a). Another narrative review examined 63 Chinese studies with a variation of acupuncture therapies in patients with rheumatoid arthritis and concluded that acupuncture is helpful for rheumatoid arthritis (Suzuki et al., 2005). However, in addition to the complexities revealed by an evaluation of this sort of intervention, many of these prior studies have methodological concerns that limit their interpretation. Therefore, this section performs an updated review of all currently available data, including Chinese publications.

### 2.2 Clinical evidence

Explanatory mechanisms from eastern and western biological theory provide a supposed rationale for the effectiveness of acupuncture to treat the chronic inflammatory nature of rheumatoid arthritis (Han et al., 1986; Han, 2004; Wang et al., 1985; Zijlstra et al., 2003). Considerable evidence has shown that acupuncture analgesia may be imitated by stimulation of nerves, which, in turn, trigger endogenous opioid mechanisms. Recent functional magnetic resonance imaging studies also demonstrated that acupuncture has regionally specific, quantifiable effects on relevant structures of the human brain (Hsieh et al., 2001; Hui et al., 2000; Napadow et al., 2005; Pariente et al., 2005; Wu et al., 1999; Yoo et al., 2004). However, clinical research into the effects of acupuncture on chronic pain is challenged by methodological concerns, including finding appropriate inactive controls. For example, the larger literature on clinical trials of acupuncture on pain has failed to show a significant improvement over sham acupuncture (Brinkhaus et al., 2006; Linde et al., 2006; Melchart et al., 2005). Indeed, there are troublesome findings of non-superiority of acupuncture over shams.

To update the current clinical evidence regarding the effects of acupuncture on rheumatoid arthritis, a comprehensive search of 10 western and Chinese databases and reference lists was performed based on our previous work (Wang et al., 2008a). The review included clinical trials with pain as an endpoint being measured by tender joint count or a pain scale. The effects of acupuncture on morning stiffness, erythrocyte sedimentation rate and C-reactive protein were also reported. Nine studies met eligibility criteria with a total of 597 subjects. There were 4 placebo-controlled trials and 5 active-controlled trials (**Table 1**). The average study duration was 11 weeks. Mean (SD) numbers of acupuncture points and sessions were 11 (8) and 42 (62), respectively. The average duration of needle insertion was 24 minutes. Eight trials used traditional acupuncture (TA) (Cui et al., 2001; David et al.,

1999; Jiang & Fan, 2003; Liu et al., 2003; Tam et al., 2007; Wang, 2002; Zanette Sde et al., 2008; Zhou & Zhu, 2000), two used electroacupuncture, (EA) (Man & Baragar, 1974; Tam et al., 2007) and one used both (Tam et al., 2007). Four trials used placebo needles (sham acupuncture or incorrectly placed needles) as the control (David et al., 1999; Man & Baragar, 1974; Tam et al., 2007; Zanette Sde et al., 2008). The other five studies published in China used a variety of active interventions in the control groups, including methotrexate, topical Votalin ointment, and non-steroidal anti-inflammatory drugs.

### 2.1.1 Placebo-controlled trials

The four placebo-controlled trials involved 160 participants. Of those, two had optimal quality and two had moderate quality (David et al., 1999; Man & Baragar, 1974; Tam et al., 2007; Zanette Sde et al., 2008). Two high quality double-blind randomized, placebo-controlled trials and two moderate quality trials evaluated the effects of either traditional or electroacupuncture versus sham acupuncture. Tam et al (2007) conducted a trial in Hong Kong among 36 patients with RA and a disease duration of 9.3 years. Patients were randomly assigned to three groups: traditional acupuncture (TA), electroacupuncture (EA), and sham acupuncture (placebo needles). Patients received a total of 20 sessions for 10 weeks using six acupuncture points. The authors found that tender joint count improved for both EA and TA groups compared with the control group (tender joint count  $\downarrow 5.5$  vs.  $\downarrow 0.5$ ,  $p < 0.05$  and tender joint count  $\downarrow 4$  vs.  $\downarrow 0.5$ ,  $p < 0.05$ , respectively). Physician's global score significantly improved for the EA group while patient's global score significantly improved for the TA group. Of note, the pain score remained unchanged in all three groups. The ACR core disease measures and DAS 28 score were not achieved at week 10.

In a contemporaneous high quality study conducted by Zanette Sde et al (2008), 40 patients with long-standing RA were randomized to traditional acupuncture or a control group using superficial acupuncture at non-acupuncture points. All participants received a total of 10 sessions, twice a week for five consecutive weeks. Tender joint count improved for the TA group compared with the control group (tender joint count  $\downarrow 8.35$  vs.  $\downarrow 2.45$ ,  $p = 0.145$ ). There was no significant difference between groups regarding ACR 20 improvement criteria (primary outcome) after the 5<sup>th</sup> and 10<sup>th</sup> sessions. At the last visit, there was a trend in favor of the acupuncture intervention compared with the control group (40% vs. 10% of each group achieved ACR20 criteria,  $p = 0.07$ , respectively). In addition, there was a significant difference favoring the TA group on physician's global assessment of the treatment ( $p = 0.012$ ), and patient's ( $p = 0.003$ ) and physician's global assessment of disease activity ( $p = 0.011$ ), but there was no difference for other endpoints. The authors concluded that the negative result could be related to the small sample size, selection of patients, type of acupuncture protocol applied, and difficulties in establishing an appropriate control group.

A double-blind randomized placebo-controlled trial conducted by David et al (1999) used a six-week crossover design comparing traditional acupuncture with sham acupuncture in 64 patients. There was a total of five weekly sessions. After a washout period of six weeks, participants were crossed-over into the other intervention arm (acupuncture or control) for an additional five weeks. The tender joint count, swollen joints count, pain scale, patient's and physician's global assessments, modified DAS, ESR, and C-reactive protein were assessed at baseline and at the end of both intervention periods. The authors found no

significant differences between the intervention and control groups for any of the endpoints at the end of both intervention periods and at the follow-up assessment.

An early RCT conducted by Man & Baragar (1974) used a parallel design among 20 participants with seropositive RA. Patients were randomly assigned to either electroacupuncture or control groups. The pain was assessed with a pain scale ranging from 0 to 4 at 24 hours after treatment. The authors reported that EA had a significant moderate and marked decrease in knee pain for 80% of the participants (60% and 20%, respectively) compared with no pain reduction in the control group. At three months, 70% of the participants in the EA group reported a significant minimal or moderate decrease in pain compared with no pain reduction in the control group. However, as no baseline data was reported, we estimated the following percentage improvements on the pain scale from the published figure (51% and 23%, at 24 hours and 3 months, respectively) for the EA group compared with no change in the control group (Man & Baragar, 1974).

### 2.1.2 Active-controlled trials

Since 2000, five active drug-controlled Chinese studies of modest quality have been conducted in China and include 468 subjects (Cui et al., 2001; Jiang & Fan, 2003; Liu et al., 2003; Wang, 2002; Zhou & Zhu, 2000). The mean study duration was 7 weeks, with 14 to 180 sessions. The number of acupuncture points varied from 8 to 24. In the control groups, two studies used indomethacin (25 mg tid for 4 weeks) (Jiang & Fan, 2003; Zhou & Zhu, 2000), one study used indomethacin (50 mg tid) plus triptolide (20 mg tid) for three weeks (Wang, 2002), one study used methotrexate (5 mg/week 1, 10 mg/week 2, 15 mg/week 3) and diclofenac (20 mg bid for 3 months) (Liu et al., 2003), and one study compared acupuncture with topical Votalin ointment (bid) (Cui et al., 2001), which may be considered as an NSAID. All five Chinese publications consistently reported that acupuncture treatment was associated with a significant decrease in pain (tender joint count mean change: -3.9) compared with controls. Three studies reported a significant reduction in morning stiffness (mean change: -29 minutes) compared with controls (Jiang & Fan, 2003; Liu et al., 2003; Zhou & Zhu, 2000). In addition, three studies observed a reduction in ESR (mean change: -5.5 mm/hour) (Jiang & Fan, 2003; Liu et al., 2003; Zhou & Zhu, 2000) and 2 noted a C-reactive protein reduction (mean change: -3.0 mg/dl) (Jiang & Fan, 2003; Zhou & Zhu, 2000), but only one showed a significant difference for ESR and C-reactive protein (Jiang & Fan, 2003). No dropouts were reported. Although these trials concluded that acupuncture was effective in relieving symptoms of RA, the long-term benefits remain unknown.

### 2.1.3 Summary of clinical evidence

Collectively, seven studies reported a decrease in pain for acupuncture compared with controls, and five showed a statistically significant improvement (Cui et al., 2001; Jiang & Fan, 2003; Liu et al., 2003; Tam et al., 2007; Zhou & Zhu, 2000). Compared with controls, the mean or median changes of acupuncture-decreased tender joint count pain ranged from 1.5 to 6.5. In addition, four studies reported a significant reduction in morning stiffness (mean change -29 minutes) but the difference was non-significant compared with controls (Jiang & Fan, 2003; Liu et al., 2003; Zanette Sde et al., 2008; Zhou & Zhu, 2000). With regards to inflammatory markers, five studies observed a reduction in ESR (mean -3.9 mm/hour) (Jiang & Fan, 2003; Liu et al., 2003; Tam et al., 2007; Zanette Sde et al., 2008; Zhou & Zhu, 2000) and three noted a reduction in C-reactive protein (mean -2.9 mg/dl) (Jiang & Fan,

2003; Zanette Sde et al., 2008; Zhou & Zhu, 2000); but only 1 study showed a significant difference for both erythrocyte sedimentation rate and C-reactive protein (Jiang & Fan, 2003).

Three decades worth of cumulative literature on acupuncture for the treatment of RA have been evaluated in both Chinese and western populations. Despite some favorable results in one placebo-controlled and 5 active-controlled trials, conflicting evidence remains regarding the efficacy of acupuncture for RA in the placebo-controlled trials. While an early RCT reported that compared to sham, 1 EA session significantly improved knee pain in 20 patients with seropositive RA (Man & Baragar, 1974), a later randomized crossover study with 56 patients with RA reported no significant differences between traditional and sham acupuncture in pain relief or inflammation (David et al., 1999). A recent systematic review which utilized these two trials in their analysis concluded that the evidence was limited due to methodological considerations, such as the type of acupuncture (acupuncture vs. electroacupuncture), the site of intervention and the small sample size of the studies included (Casimiro et al., 2005).

All five active comparator trials published in China concluded that acupuncture treatment was associated with a significant decrease in tender joint count and was effective in relieving other symptoms of RA compared with controls. However, the methodological limitations of the Chinese studies included inappropriate control interventions (non-comparable), no double-blind interventions, inadequate description of the randomization process, and scarce use of validated outcome measures. The Chinese studies also used active drugs in place of placebo acupuncture, which makes comparisons across studies difficult.

Accurate quantitative estimates of treatment effects were not obtained due to the heterogeneity of the studies, as well as differences in acupuncture interventions, including dose/intensity and treatment duration. For instance, the number of acupuncture points ranged from 1 to 24, the duration of needle insertion ranged from 4 to 40 minutes, and the number of sessions varied from 1 to 180. The time elapsed between sessions also fluctuated.

For all these reasons, the evidence for the efficacy of acupuncture for pain relief in RA is modest and uncertain. Furthermore, the long-term benefits remain unknown. Because it is difficult to compare such divergent trials and there is a lack of standardized treatment protocols, future studies should focus on the optimum dose for acupuncture therapy in persons with RA, such as effective evidence-based dose/intensity, and number of acupuncture points, duration of needle insertion, frequency of acupuncture sessions, and intervention duration. It is possible that some studies, while designed correctly from a western scientific approach, do not have the correct Chinese medical approach (i.e. inappropriate dose/intensity and duration of acupuncture, insufficient expertise of acupuncturist leading to inappropriate needle insertion and manipulation techniques, or inappropriate acupuncture point selection by a standardized protocol that may neglect the individualized Chinese medical diagnosis). These reasons might explain why no specific effects were observed in western studies.

This comprehensive review of acupuncture for rheumatoid arthritis illustrates the need for methodologically rigorous acupuncture study designs that adhere to both the high standards of western scientific randomized controlled trials and accommodate the correct Chinese medical approach. Further research is needed to understand the effects of acupuncture on RA and how patients may or may not benefit from its inclusion in their treatment.

Ref.	RA Patients	Duration (weeks)	Acupuncture	Control*	Findings <sup>a</sup>
<b>Placebo-controlled Randomized Controlled Trials</b>					
Tam, 2007 Hong Kong	Active RA, mean disease duration 9.3 years N= 36 Age= 58	10	Group 1: EA Group 2: TA (20 sessions) Needle insertion time: 30 min	Sham acupuncture Placebo needles (20 sessions)	EA: ↓ 5.5 TA: ↓ 4 Control group: ↓ 0.5 Difference between groups at week 10: EA vs. control: ↓ 5.0 TA vs. control: ↓ 3.5
Zanette Sde, 2007 Brazil	RA for at least 6 months with stable drug treatment for at least 1 month N= 40 Age>50	9	TA (10 sessions) Needle insertion time: 20 min	Superficial acupuncture at non-acupuncture points (10 sessions)	TA: ↓ 8.35 Control group: ↓ 2.45 Difference between groups: ↓ 5.9
David, 1999 UK	RA, mean disease duration 10 years. N= 64 Age=18-75	22	TA (5 sessions) Needle insertion time: 4 min	Placebo needles (5 sessions)	Treatment effect: ↑ 0.5 (-1, 1.5)**
Man, 1974 Canada	Patients with seropositive RA for ≥ 5 years, for whom bilateral knee pain was a major problem N= 64 Age=18-75	16	EA (3 AP/ 1 session) Needle insertion time: 15 min	Placebo needles (1 session)	EA (24h): 51% improvement EA (3 months): 23% improvement Control group: 0% improvement in pain scale (0-4)
<b>Randomized Controlled Trials Compared to Active Comparators</b>					
Liu, 2003 China	RA with mean disease duration 3.6 years. N= 240 Age=42	12	TA (180 sessions) Needle insertion time: 30 min	Methotrexate IM injection - week 1: 5 mg - week 2: 10 mg - week 3: 15 mg + Diclofenac (20 mg/day)	TA: ↓ 16.6 Control group: ↓ 10.1 Difference between groups: ↓ 6.5
Jiang, 2003 China	Functional class 1 and 2 patients with RA with	4	TA (15 sessions)	Indomethacin (25 mg tid)	TA: ↓ 5.1 Control group: + 0.6

	mean disease duration 4.5 years. N= 60 Age=45		Needle insertion time: 30 min		Difference between groups: ↓ 4.5
Wang, 2002 China	RA with mean disease duration 10 years. N= 61 Age=ND	3	TA (14 sessions) Needle insertion time: 30 min	Indomethacin (50 mg tid) plus triptolide (20 mg tid)	Significant improvement of total effective rate
Cui, 2001 China	RA (1987 ACR criteria and no data for disease duration. N= 60 Age=ND	12	TA (90 sessions) Needle insertion time: 20-30min	Votalin ointment (bid) <sup>b</sup>	TA: ↓ 8.3 Control group: ↓ 6.8 Difference between groups: ↓ 1.5
Zhou, 2000 China	Functional class 1 and 2 patients with RA, with mean disease duration 3 years N= 45 Age=18-65	4	TA (15 sessions) Needle insertion time: 40 min	Indomethacin (25 mg tid)	TA: ↓ 7.1 Control group: 4.0 Difference between groups: ↓ 3.1

Abbreviations: EA= electro acupuncture; TA= traditional acupuncture; ND= No data; RA=Rheumatoid arthritis;

<sup>a</sup>Mean or median difference or improvement was calculated between groups and confidence interval cannot be calculated from published data. <sup>b</sup> Votalin ointment components not reported. \*Sham acupuncture: needles inserted up to 2 mm, shorter insertion duration, and minimal needle stimulation. \*\*Median difference.

Table 1. Randomized Controlled Trials Evaluating the Effect of Acupuncture on RA

### 3. Mind-body therapy for rheumatoid arthritis

#### 3.1 Tai Chi mind-body therapeutics

In the past two decades, the literature has consistently recognized the potential therapeutic benefits of Tai Chi mind-body exercise. Significant improvements have been reported in balance, strength, flexibility, cardiovascular and respiratory function, mood, depression and anxiety, self-efficacy, pain reduction and health-related quality of life in diverse eastern and western populations for a variety of chronic conditions (Wang et al., 2004). Several recent reviews have further suggested that Tai Chi appears to improve a variety of medical conditions (Adler & Roberts, 2006; Jahnke et al., 2010; Rogers et al., 2009; Wang et al., 2010a; Yeh et al., 2009).

Tai Chi, a traditional Chinese mind-body exercise, has grown in popularity in the United States. According to the 2007 National Health Interview Survey, around 2.5 million



Americans have practiced Tai Chi for health reasons and that number is increasing (Barnes et al., 2009). Furthermore, individuals with musculoskeletal conditions are more likely to practice Tai Chi (Birdee et al., 2009). It is clear that our patients with rheumatic disease are interested in seeking this type of complementary and alternative treatment. Thus, it is important to examine the evidence base for mind-body medicine to provide the clinician with an overview of these new sources of knowledge for the best care for our rheumatic patients.

### 3.2 Scientific evaluation of Tai Chi for rheumatoid arthritis

One early publication by Kirsteins and colleagues reported on two non-randomized controlled trials of 47 and 28 rheumatoid arthritis patients with 10 weeks Tai Chi training. Disease activity (joint tenderness, number of swollen joints), 50 foot walks, handgrip strength, a written functional assessment, and exacerbation of joint symptoms were measured. The studies showed that Tai Chi appears to be safe for rheumatoid arthritis patients and may serve as a suitable weight-bearing exercise with the additional potential advantages of stimulating bone growth and strengthening connective tissue (Kirsteins et al., 1991).

Two randomized controlled trials were recently published in Korea. A study of 31 patients reported by Lee showed that compared with a usual care group, 6 weeks of Tai Chi training significantly improved mood and sleep disturbance (Lee, 2005). Another trial of 61 patients showed that 50 minutes per week of Tai Chi training for 12 weeks significantly decreased pain and fatigue compared to usual care controls (Lee & Jeong, 2006).

To obtain preliminary data on the effects of Tai Chi on rheumatoid arthritis, the author's research group conducted a pilot randomized controlled trial (Wang, 2008b). Twenty patients with functional Class I or II rheumatoid arthritis were randomly assigned to Tai Chi or attention control in twice-weekly sessions for 12 weeks. The American College Rheumatology 20 response criteria, functional capacity, health-related quality of life and the depression index were assessed. At 12 weeks, 5/10 patients (50%) randomized to Tai Chi achieved an American College Rheumatology 20% response compared with 0/10 (0%) in the control ( $p = 0.03$ ). Tai Chi had greater improvement in the Disability Index ( $p = 0.01$ ), Vitality subscale of the SF-36 ( $p = 0.01$ ) and the Depression Index ( $p = 0.003$ ). Similar trends to improvement were also observed for disease activity, functional capacity and health related quality of life. No adverse events were observed and no patients withdrew from the study, suggesting that Tai Chi is safe and may be beneficial for Functional Class I or II rheumatoid arthritis.

A subsequent study of Tai Chi in rheumatoid arthritis patients by Uhlig and colleagues, however, has produced inconsistent results. A with-in group comparison study involving 15 female patients with rheumatoid arthritis aged 40-70 years, participating in 8-week Tai Chi training showed no improvements in disease activity, muscle strength, flexibility, balance and health status (Uhlig et al., 2005). The second study from the same group of investigators overcame the previous limitations, using a 12-week Tai Chi program for another 15 patients. They found that Tai Chi improved lower-limb muscle function and endurance at 12 weeks follow-up (Uhlig et al., 2010). A Cochrane review, examining the evidence from 4 clinical trials, suggested that Tai Chi does not exacerbate symptoms of rheumatoid arthritis and has some benefits on lower extremity range of motion for people with rheumatoid arthritis, in particular ankle range of motion (Han et al., 2004).

Chronic pain in rheumatoid arthritis is commonly accompanied by psychosocial stress, anxiety and depression. Therapeutic approaches with psychological and behavioral impact, such as Tai Chi mind-body therapy, could better patients' emotional health outcomes (Bradley & Alberts, 1999).

The author's group systematically reviewed the evidence of the effects of Tai Chi on stress, anxiety, depression and mood disturbance in various eastern and western populations (Wang et al., 2010a). Specifically, the results of 33 randomized and nonrandomized trials suggest that regular Tai Chi practice is significantly associated with improvements in psychological well-being including reduced stress (effect size, 0.66; 95% confidence interval [CI], 0.23 to 1.09), anxiety (effect size, 0.66; 95% CI, 0.29 to 1.03), depression (effect size, 0.56; 95% CI, 0.31 to 0.80), and mood disturbance (effect size, 0.45; 95% CI, 0.20 to 0.69) in healthy participants and patients with chronic conditions. Seven observational studies with relatively large sample sizes reinforced the beneficial association between Tai Chi practice and psychological health. Notably, the review found that Tai Chi tended to reduce depression compared to various controls among individuals with osteoarthritis (Fransen et al., 2007; Wang et al., 2009), rheumatoid arthritis (Wang, 2008b) fibromyalgia (Taggart et al., 2003; Wang et al., 2010b), depression disorders (Chou et al., 2004), sedentary obese women (Dechamps et al., 2009), and elderly participants with cardiovascular disease risk factors (Taylor-Piliae et al., 2006). This positive result was associated with improvement in symptoms and physical function in patients with rheumatoid arthritis and other chronic conditions. Interestingly, the benefits were also associated with an improvement in the immune response. A 50% improvement in varicella zoster virus-specific cell-mediated immunity (T cell-dependent response) after 15 and 25 weeks of Tai Chi in healthy elderly Americans (Irwin et al., 2003; Irwin et al., 2007) was observed.

However, the vast majority of the studies suffer from less rigorous designs with only two studies reporting results on participants diagnosed with clinical depression. Nevertheless, the potential mental health benefits of Tai Chi mind-body therapy support its inclusion as a key component of a multidisciplinary medical approach to promote psychological health, treat chronic pain, and better inform clinical decision-making for rheumatoid arthritis.

As a chronic disorder characterized by inflammation leading to joint destruction, rheumatoid arthritis has increased clinically important comorbidities including cardiovascular complications and osteoporosis. Numerous studies have evaluated the effects of Tai Chi on cardiovascular and respiratory function (Lai et al., 1993; Lai et al., 1995; Lan et al., 1996; Lan et al., 1998; Lan et al., 1999). Since 1979, results related to the effect of Tai Chi on cardiovascular and pulmonary function have been reported in 43 eastern and western publications (Wang et al., 2004; Yeh et al., 2008; Yeh et al., 2009). Among them, one study (Zhuo et al., 1984) reported that the metabolic intensity of the activity seems insufficient to generate improvements of cardiorespiratory fitness in healthy young adults. Yet, all other studies suggested that regular Tai Chi practice may preserve cardiorespiratory function in older individuals and may be prescribed as a suitable exercise for older adults. Our systematic reviews of literature have shown that Tai Chi can reduce blood pressure and increase cardiovascular exercise capacity (Yeh et al., 2008; Yeh et al., 2009). A very recent large single-blind, multisite, randomized controlled trial evaluated a 12 week Tai Chi exercise in patients with heart failure (Yeh et al., 2011). At completion of the study, patients in the Tai Chi group had greater improvements in quality of life ( $P=0.02$ ), exercise self-efficacy ( $P<0.001$ ) and mood ( $P=0.01$ ). The authors concluded that Tai Chi exercise, a multi-component mind-body training modality that is safe and has good rates of adherence, may provide value in improving daily exercise, quality of life, mood, and exercise self-efficacy in patients with chronic heart failure. Thus, encouraging evidence suggests that Tai Chi may be a safe and beneficial adjunctive therapy to conventional care for patients with rheumatoid arthritis-associated cardiovascular disease and related complications.

Taken together, these trials show that Tai Chi may provide some important components in the treatment of Rheumatoid Arthritis. Further research should focus on ideal dose and duration of intervention to provide valuable information about how Tai Chi may be best used in clinical practice.

#### **4. Benefit of tripterygium wilfordii hook F in patients with rheumatoid arthritis**

##### **4.1 Tripterygium wilfordii hook F therapeutics**

In traditional Chinese medicine, extracts of the roots of *Tripterygium Wilfordii* Hook F (TwHF, *Lei Gong Teng*) has been widely used for the treatment of autoimmune and inflammatory disease in China. Several clinical trials have examined the therapeutic effects of TwHF in patients with rheumatoid arthritis (Cibere et al., 2003; Goldbach-Mansky et al., 2009; Tao et al., 2001; Tao et al., 2002; Vitetta et al., 2008). In an early nonrandomized controlled clinical trial, Tao and colleagues evaluated 13 patients with established rheumatoid arthritis who received a maximum dosage of 180 mg/day of TwHF. There were no adverse effects or disease improvements observed at that dosage and nine patients tolerated the extract up to a dosage of 570 mg/day. Eight of the nine patients who received the extract at doses over 360 mg/day experienced improvement in both clinical manifestations and laboratory findings and one patient met American College of Rheumatology criteria for remission (Tao et al., 2001). The results of this small trial suggested that the ethyl acetate extract of the Chinese herbal remedy was safe with tolerable side effects for most patients with rheumatoid arthritis who achieved clinical benefits. Subsequently, the same group of investigators used a prospective, double-blind, placebo-controlled trial for another 35 patients and found that eight patients in the 20-week low-dose (180 mg/day) group and four patients in the high-dose (360 mg/day) group met criteria for clinical response. The authors also concluded that the ethanol/ethyl acetate extract of TwHF, at a dosage of 360 mg/day, appeared to be safe in patients with rheumatoid arthritis (Tao et al., 2002). Another Chinese randomized double-blind placebo-controlled trial of 61 patients with rheumatoid arthritis suggested that six weeks of TwHF significantly improves American College of Rheumatology 20% response rate compared with placebo (TwHF 58% vs placebo 20%;  $P=0.002$ ) (Cibere et al., 2003).

Recently, to compare the benefits and side effects of TwHF extract with those of sulfasalazine, a large randomized, controlled trial of 121 patients with active rheumatoid arthritis used TwHF extract 60mg, three times daily or sulfasalazine 1g, twice daily. Patients could continue stable doses of oral prednisone and non-steroidal anti-inflammatory drugs but not disease-modifying antirheumatic drugs. Among patients who continued treatment for 24 weeks, achievement of 20% improvement in American College of Rheumatology criteria was greater with TwHF than with sulfasalazine. Adverse event rates were similar. Also, patients receiving TwHF had significantly higher response rates for American College of Rheumatology 50% and American College of Rheumatology 70% criteria. In the TwHF group, significant improvement was demonstrated in all individual components of the American College of Rheumatology response, including the Health Assessment Questionnaire score. Interleukin-6 levels rapidly and significantly decreased in the TwHF group (Goldbach-Mansky et al., 2009).

The long-term effects and toxicities of TwHF and the potential combination of TwHF with other antirheumatic therapies need to be further investigated. However, evidence demonstrates that treatment with a standardized extract from the peeled roots of the

Chinese herbal remedy TwHF administered from four weeks to over 24 weeks may be both effective and safe in treating patients with active rheumatoid arthritis.

### **5. Tibetan Five Nectar Formula medicated bath therapy for pain relief in patients with RA**

Tibetan Five Nectar Formula is derived from five types of plants and has been considered to have anti-inflammatory and immunomodulating effects for rheumatoid arthritis when used as bath therapy. To understand the beneficial effect of Tibetan Five Nectar Formula Medicated-Bath Therapy on patients with rheumatoid arthritis, the author's research group has recently conducted a comprehensive review of the literature of Tibetan Five Nectar Formula Medicated-Bath Therapy on patients with rheumatoid arthritis (Jacobson et al., 2010).

Eighty-seven potentially relevant studies were identified. Nine non-randomized controlled trials of 757 subjects met eligibility criteria (Jacobson et al., 2010). All the trials were conducted in the Tibetan area of China and used the Five Nectar formula in the Tibetan Medicated-Bath. Bath temperatures were of 35-46 °C for 10-15 min, once or twice a day. Mean treatment duration ranged from 7-30 days per course, for 1-3 courses. Two studies stopped some or all western medications during treatment. The 9 studies also used supplemental oral Tibetan herbal therapy. The effect of the Tibetan Five Nectar Formula Medicated-Bath Therapy on clinical symptoms was measured with Physician-assessed composite outcomes. All studies reported a positive association between the Tibetan Five Nectar Formula Medicated-Bath Therapy and improved clinical pain symptoms within group comparisons. In addition, three studies reported an improvement in immune function. There are discordant trial designs and lack of reported qualitative outcomes measure were among other methodological limitations. The overall study quality was poor with no controls or randomization, blinding or reports of dropout rates. However, these studies suggest that Tibetan Five Nectar Formula Medicated-Bath Therapy may be helpful in the treatment of pain symptoms due to rheumatoid arthritis. However, they are of only weak evidentiary value due to uniformly poor methodological quality. Future studies with more rigorous design and adequate statistical analysis are warranted.

### **6. Conclusion**

In summary, as a complex immunologically mediated disorder, rheumatoid arthritis is still a therapeutically challenging chronic condition to control. Emerging evidence from clinical trials reviewed here support that evidence-based complementary and alternative medicine or integrative medicine therapies may offer effective treatments for patients with Rheumatoid Arthritis. Integrative approaches combine the best of conventional medicine and the wisdom of complementary and alternative medical approaches. These modalities may lead to the development of better lifestyle modifying strategies, while mind-body medicine such as Tai Chi exercise could affect progression of disease and decrease morbidity and mortality among individuals with rheumatoid arthritis. While existing evidence regarding complementary and alternative medicine on rheumatoid arthritis remains limited and inconclusive, the promising results suggest that these complementary and alternative medicine treatments may be a safe adjunctive therapy for rheumatoid arthritis and warrant further exploration.

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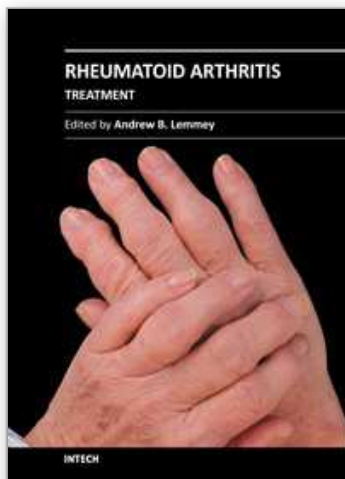
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## **Rheumatoid Arthritis - Treatment**

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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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