

EFFECTS OF ACUPUNCTURE ON RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW AND
META-ANALYSIS

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Abstract

Background: The aim of this study was to evaluate the efficacy of acupuncture for treating rheumatoid arthritis (RA).

Methods: The literature were searched using 6 databases, including Pubmed, Embase, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, VIP and Wanfang database up to December 2013, without language restrictions. All randomised clinical trials (RCTs) comparing acupuncture treatment with non-acupuncture treatment of RA was considered. Methodological quality was assessed using the Jadad score.

Results: After strict screening, a total of 21 studies containing 1772 participants were included. The meta-analysis indicated that a significant benefit of acupuncture compared with non-acupuncture on improving the symptoms of RA (pooled $RR = 1.19$, 95% CI 1.08–1.31, $Z = 3.47$, $P = 0.001$). In the subgroup analysis, 9 RCTs showed significant effects of acupuncture for response rate compared with western medicine ($RR = 1.26$, 95% CI 1.02–1.55, $Z = 2.19$, $P = 0.028$); 5 RCTs showed significant effects of acupuncture plus traditional Chinese drug compared with traditional Chinese drug ($RR = 1.17$, 95% CI 1.07–1.29, $Z = 3.31$, $P = 0.001$); 5 RCTs showed beneficial effects of acupuncture plus western medicine compared with western medicine ($RR = 1.27$, 95% CI 1.06–1.53, $Z = 2.56$, $P = 0.01$).

Conclusion: This meta-analysis demonstrates that acupuncture may have a favourable effect on treating RA. However, the evidence was limited by the small sample size and the low methodological quality. Considering the potential of acupuncture, more researches and well-designed, rigorous and large clinical trials are needed.

Key words: Traditional Chinese Medicine, Acupuncture, Rheumatoid arthritis, Meta-analysis

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory systemic autoimmune disease, affecting approximately 1% of the population worldwide (Gibofsky, 2014). It is mainly characterized by synovial hyperplasia in peripheral joints and results in progressive destruction of articular structures. Due to the clinical symptoms and long duration, RA has a negative effect on the ability to work and health-related quality of life. In addition, the treatment of this disease and associated complications inflict heavy economic burden to the society and families (Marra et al., 2011). It has been estimated that the life expectancy of persons with RA may be reduced by 5-10 years and mortality is increased more than twofold when compared to non-affected individuals (Kvien, 2004; Sommer et al., 2005). Therefore, RA has been considered as one of the major global public health problems.

The aetiology and pathogenesis of RA have yet to be established, existing evidence suggests that genetic and environmental factors might contribute to the development of this disease (McInnes and Schett, 2011). The complex, systemic nature of RA makes

it difficult to cure. The main goals of the treatment on RA are to prevent articular damage and functional loss by decreasing the activity of the disease. To date, a wide range of pharmacological and non-pharmacological therapies have been used in the treatment of RA. Among all these methods, traditional Chinese medicine (TCM) takes great advantage on this disease and has been considered as an important strategy. Acupuncture is the typical representative of TCM and known as one of the most commonly used forms of complementary and alternative medicine (Casimiro et al., 2005; Moudgil and Berman, 2014).

Acupuncture is the insertion and stimulation of needles at specific points on the body for therapeutic or preventive purposes (Vickers et al., 2012). It has a history of more than 3000 years and has been used in many countries for treating various diseases, although its mechanisms of action remain unknown. Acupuncture not only has the value of treatment, but also has few side effects (Odsberg et al., 2001). In the last decade, numerous studies in China (Ai et al., 2005; Chen, 2012; Ma and Gao, 2013; Ma and Li, 2008) showed favorable effects for acupuncture in treatment of RA, but most were just clinical observations on the therapy. Acupuncture remains steeped in controversy. Some findings are encouraging but others suggest that its clinical effects mainly depend on a placebo response (Ernst, 2006). Therefore, we conducted a systematic review and meta-analysis to summarize and critically assess whether acupuncture is effective as a means of treating RA.

Materials and Methods

Criteria for Including Studies

All randomized controlled trials (RCTs) comparing acupuncture treatment with non-acupuncture treatment of RA was considered. To be selected for analysis, a study had to meet all of the following criteria: (1) Types of participants: all patients of these studies fulfilled the diagnostic criteria for RA; (2) Types of interventions: in the treatment group, acupuncture included needle acupuncture, ear acupuncture, fire acupuncture, and electro-acupuncture. Trials testing other forms of acupuncture, such as bee venom acupuncture, abdominal acupuncture or moxibustion were excluded. Acupuncture combined with other treatment could be included on condition that the control group received the same concomitant treatments as the acupuncture group. Those comparing two different forms of acupuncture were excluded; (3) the study reported changes or improvements in the symptoms of RA as outcome measures.

Search Strategy

The following databases were searched up to December 2013 without language restrictions: PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), VIP database and Wanfang database. The search terms including “acupuncture” OR “acupuncture therapy” OR “acupuncture points” AND “rheumatoid arthritis” OR “RA” were used in the search strategy. The reference lists of all included studies were also screened for potentially relevant papers.

Data Extraction and Quality Assessment

Data extraction was performed independently by two investigators. The information including first author’s name, year of publication, the number of patients, duration of the intervention, outcomes were extracted for each included study. If there was disagreement, it was resolved by discussion with our research team.

The quality of the studies included in the meta-analysis was assessed according to a standard scoring system proposed by Jadad et al (Jadad et al., 1996). The assessment was based on: (1) whether the randomization method was appropriate; (2) whether double blindness was mentioned in the trial and whether the trial was appropriately performed; and (3) whether the number of patients who withdrew, and their reasons, were clearly stated. The scores ranged from 0 to 5 with higher scores denoting better quality of a trial. The studies were regarded as low-quality if the score was 2 or less and high-quality if the score was at least 3 (Kjaergard et al., 2001;

Moher et al., 1998).

Outcome Measures and Data Synthesis

All clinical endpoints were considered, but the primary outcome measure was the response rate for treating symptoms in patients with RA. The effect for each intervention was generally divided into four categories, including (1) recovery, (2) marked improvement, (3) improvement, and (4) no change. The effective rate of improvement in two groups was calculated using the following formula: effective rate = (recovery + marked improvement + improvement) / total number. We did not evaluate the outcomes related to immunological or other surrogate endpoints due to lack of complete data.

The differences between the treatment and control groups were assessed. Relative risk (*RR*) and 95% confidence intervals (*CI*s) were calculated. Heterogeneity of the trials was assessed by means of the χ^2 and I^2 tests. The pooled statistics were calculated using the fixed-effect model, and a random-effect model was used if the *P* value of the heterogeneity test was < 0.1. The two-tailed *P* values less than 0.05 were considered statistically significant. All statistical analysis was performed using STATA 11.0 software.

Results

Study Selection and Characteristics of Eligible Studies

Of 1869 screened articles, a total of 21 trials were included in the meta-analysis (Ai et al., 2005; Chen et al., 2012; Chen, 2012; Chen and Le, 2005; Cheng, 2006; Ding et al., 2011; He and Cai, 2011; Li and Li, 2010; Liu, 2006; Liu et al., 2003; Ma and Gao, 2013; Ma and Li, 2008; Shen et al., 2012; Tan, 2010; Tian et al., 2005; Wang, 2010; Wang and Li, 2008; Wang, 2002; Wu et al., 2002; Zhou and Li, 2012; Zuo et al., 2004). The detailed study selection processes are shown in Fig. 1. All these studies were conducted in China and the results published in Chinese. Totally, 1772 patients were involved in this analysis, 975 patients in the treatment group and 797 patients in the control group. Among all the RCTs included, 9 RCTs compared the therapeutic effects of acupuncture with western medicine (Chen, 2012; He and Cai, 2011; Liu et al., 2003; Ma and Gao, 2013; Shen et al., 2012; Tan, 2010; Wang, 2002; Wu et al., 2002; Zhou and Li, 2012). 5 studies examined the effect of acupuncture combined with traditional Chinese drug vs traditional Chinese drug (Chen et al., 2012; Chen and Le, 2005; Cheng, 2006; Liu, 2006; Zuo et al., 2004). 5 RCTs tested acupuncture combined with western medicine vs western medicine (Ai et al., 2005; Li and Li, 2010; Ma and Li, 2008; Wang, 2010; Wang and Li, 2008). 1 RCT compared the effect of acupuncture with traditional Chinese drug (Ding et al., 2011). 1 RCT tested acupuncture combined with Chinese and western drugs union, vs Chinese and western drugs union (Tian et al., 2005). Table 1 provides a descriptive summary of the studies included in the review.

Quality Assessment of the Included Studies

The quality of reporting in the studies included was poor. Although all these studies had a statement regarding randomization, few of them gave sufficient information on how the random allocation was generated such as from random number table, calculator or computer random number generator. Furthermore, only one study (Chen et al., 2012) described patient or assessor blinding, details of drop-outs and withdrawals, which met our criteria for higher quality. The Jadad score of included studies were listed in Table 1.

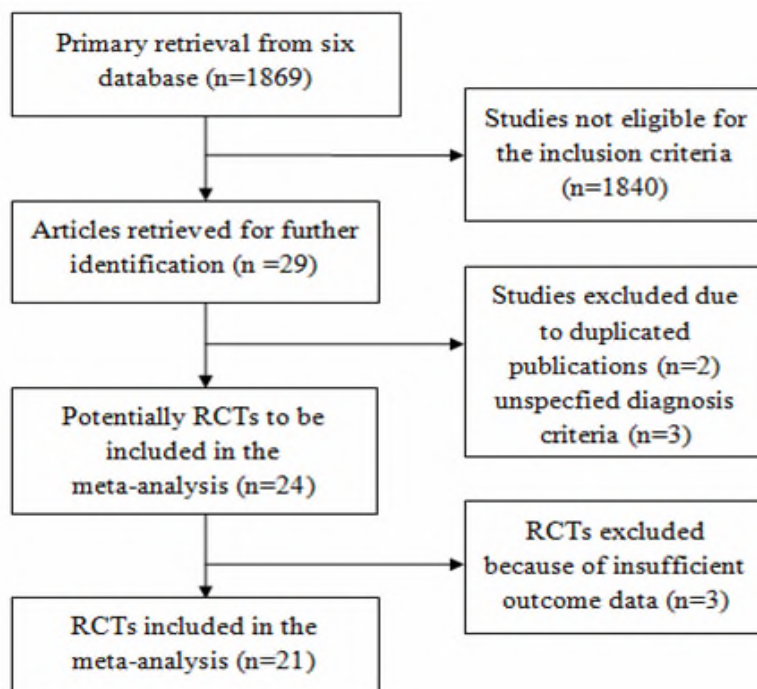
Meta-Analysis

Combined Analysis

When pooled, substantial heterogeneity was present in the comparison between the treatment group and the control group ($I^2 = 79.2\%$, $P < 0.01$), thus we conducted analyses using the random effect model. The results from 21 RCTs showed a significant benefit

of acupuncture on improving the symptoms of RA (pooled $RR = 1.19$, 95% CI 1.08–1.31, $Z = 3.47$, $P = 0.001$), as shown in Fig. 2.

Figure 1: Flow chart of trial selection process



Subgroup Analysis

Acupuncture vs. Western Medicine

In total, 9 studies including 700 patients were analyzed in this subgroup analysis. Substantial heterogeneity existed in the comparison between acupuncture and western medicine ($I^2=85.9\%$, $P < 0.01$). The meta-analysis showed favourable effects of acupuncture on response rate ($RR = 1.26$, 95% CI 1.02–1.55, $Z = 2.19$, $P = 0.028$, Fig. 3).

Table 1: Summary of randomised clinical studies of acupuncture for RA

First author (year)	Cases	Treatment group			Control group			Jadad
		sample size	type of intervention	duration of intervention	sample size	type of intervention	duration of intervention	
Ma XP (2013)	69	39	fire acupuncture	6 weeks	30	western medicine	6 weeks	1
Chen H (2012)	52	26	electroacupuncture+ traditional Chinese drug	3 months	26	traditional Chinese drug	3 months	4
Shen T (2012)	56	28	fire acupuncture	10 weeks	28	western medicine	3 months	2
Zhou YF (2012)	60	30	electroacupuncture	3 months	30	western medicine	3 months	2

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Chen JY (2012)	80	40	fire acupuncture	8 weeks	40	western medicine	8 weeks	1
Ding J (2011)	86	43	acupuncture	1 month	43	traditional Chinese drug	1 month	2
He CG (2011)	60	30	acupuncture	2 months	30	western medicine	2 months	2
Li Y (2010)	80	40	acupuncture+ western medicine	1 month	40	western medicine	1 month	1
Tan LM (2010)	84	45	fire acupuncture	10 weeks	39	western medicine	1 month	2
Wang SF (2010)	80	40	acupuncture	1 month	40	western medicine	6 months	1
Ma ZY (2008)	80	40	electroacupuncture+ western medicine	1 month	40	western medicine	1 month	1
Wang SF (2008)	68	38	acupuncture+ western medicine	1 month	30	western medicine	6 months	1
Liu L (2006)	86	52	Acupuncture+ traditional Chinese drug	1 month	34	traditional Chinese drug	1 month	1
Cheng LH (2006)	64	33	electroacupuncture+ traditional Chinese drug	1 month	31	traditional Chinese drug	1 month	1
Tian SS (2005)	100	60	acupuncture+Chinese and western drugs union	6 months	40	Chinese and western drugs union	6 months	1
Ai Z (2005)	146	74	electroacupuncture+ western medicine	1 month	72	western medicine	1 month	2
Chen RL (2005)	90	60	acupuncture+ traditional Chinese drug	2 months	30	traditional Chinese drug	2 months	2
Zuo F (2004)	100	62	acupuncture+ traditional Chinese drug	15 days	38	traditional Chinese drug	15 days	2
Liu LG (2003)	98	49	electroacupuncture	20 days	49	western medicine	20 days	2
Wu HD (2002)	84	45	fire acupuncture	1-3 months	39	western medicine	1-3 months	1
Wang YJ (2002)	109	61	acupuncture	7-15 days	48	western medicine	NA	1

NA, not available

Figure 2: Meta-analysis of acupuncture versus non-acupuncture for RA

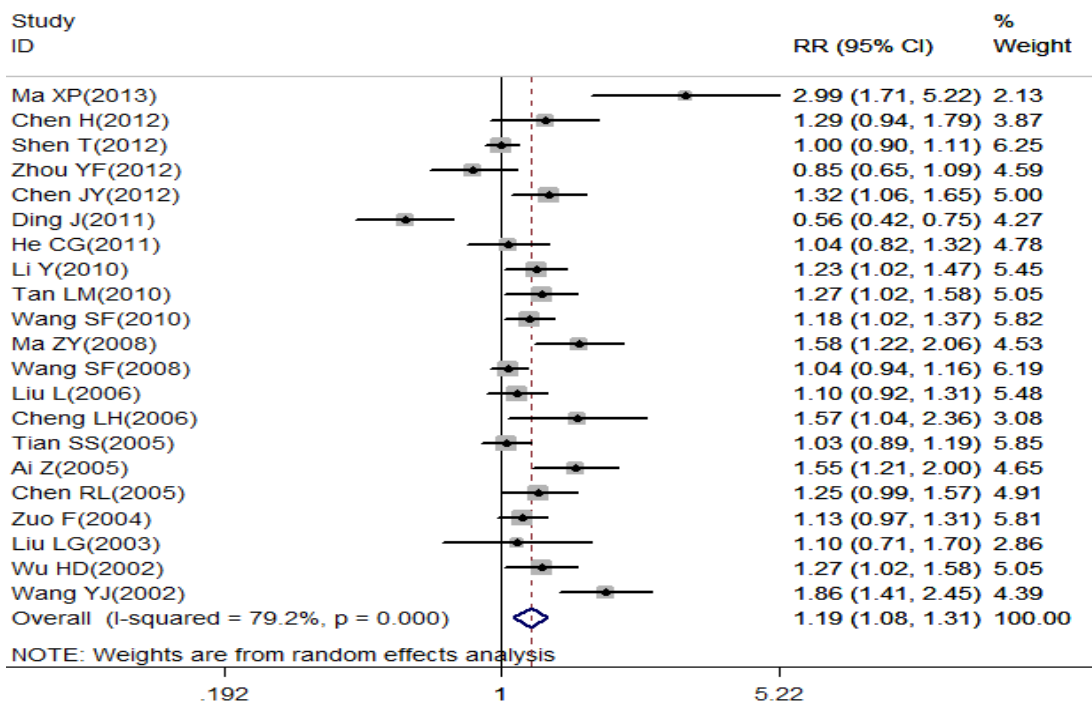
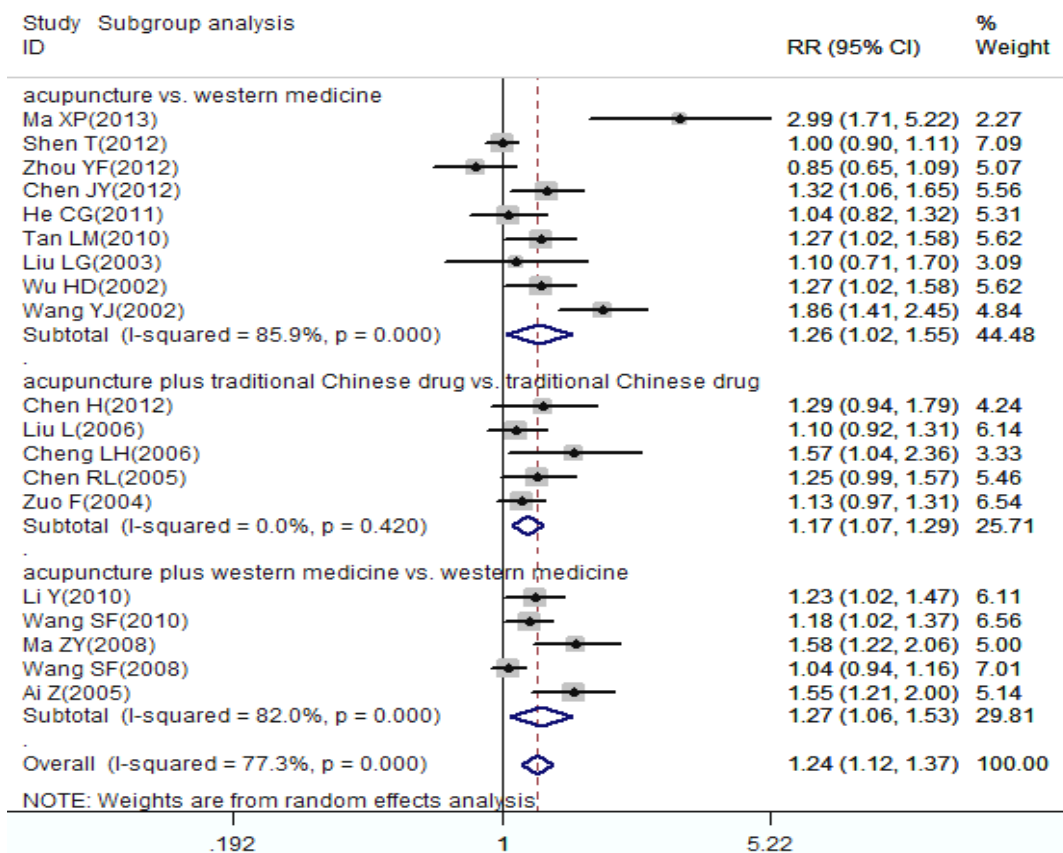


Figure 3: Subgroup analysis of acupuncture versus non-acupuncture for RA



Acupuncture plus Traditional Chinese Drug vs. Traditional Chinese Drug

5 studies including 392 patients were involved in this subgroup analysis. No heterogeneity existed in the comparison between

acupuncture plus traditional Chinese drug and traditional Chinese drug ($I^2 = 0\%$, $P = 0.42$). Pooled results showed that there was a statistically significant difference between these two groups ($RR = 1.17$, 95% CI 1.07–1.29, $Z = 3.31$, $P = 0.001$, Fig. 3). The therapeutic effect of acupuncture plus traditional Chinese drug is superior to traditional Chinese drug.

Acupuncture plus Western Medicine vs. Western Medicine

5 RCTs including 494 patients were analyzed in this subgroup analysis. Substantial heterogeneity was present in the comparison between acupuncture combined with western medicine and western medicine ($I^2 = 82.0\%$, $P < 0.01$). The meta-analysis showed favourable effects of acupuncture plus western medicine on response rate ($RR = 1.27$, 95% CI 1.06–1.53, $Z = 2.56$, $P = 0.01$, Fig. 3).

Acupuncture vs. Traditional Chinese Drug

1 RCT tested the effect of acupuncture compared with traditional Chinese drug (Ding et al., 2011). This study indicated that the curative effect of traditional Chinese drug is significantly superior to acupuncture.

Acupuncture plus Chinese and Western Drugs Union vs. Chinese and Western Drugs Union

1 RCT compared the effect of acupuncture plus Chinese and western drugs union with Chinese and western drugs union alone. This study showed these two therapy methods could significantly improve the symptoms with RA. However, there was no significant difference between them on response rate.

Adverse Effect

Three of the studies reported adverse effects during the process of the treatment of RA (Ai et al., 2005; Chen et al., 2012; Ding et al., 2011). One study reported that the incidence of adverse reactions in the group using acupuncture combined with traditional Chinese drug was significantly less than that of the group using traditional Chinese drug alone (Chen et al., 2012). The other two studies found no significant differences in the frequency of adverse event between acupuncture and medication (Ai et al., 2005; Ding et al., 2011). Most of the minor adverse events including abnormal liver function, gastrointestinal reaction and oral ulcer were resolved by the end of treatment. Except one RCT (Ai et al., 2005) reported that two patients withdrew from medication treatment due to adverse events, no serious adverse events were reported in the acupuncture treatment.

Discussion

Acupuncture was developed in ancient China and its first written description appears in the Yellow Emperor's Classic of Medicine (Amezaga Urruela and Suarez-Almazor, 2012). Acupuncture, one of the prominent methods in alternative medicine, is receiving increasing acceptance in Western medicine for treating certain medical conditions. Up to now, acupuncture is widely used for the treatment of many rheumatic diseases, including RA (Amezaga Urruela and Suarez-Almazor, 2012; Berman et al., 2000; Ernst and Lee, 2010). However, the evidence for the efficacy of acupuncture in the treatment of RA is inconclusive. A few systematic reviews have been published evaluating RCTs of acupuncture in RA patients. A Cochrane review in 2005 included 2 RCTs examining the effects of acupuncture on disease activity in 84 patients with RA (Casimiro et al., 2005). The result showed that the acupuncture treatment was not statistically significantly superior to the control intervention on pain, general health, disease activity and so on. Another review in 2008 (Lee et al., 2008) including 8 RCTs of patients with RA treated with acupuncture with or without electrical stimulation or moxibustion. The result failed to show specific effects of acupuncture for treating RA. On the contrary, a review including 11 studies (9 RCTs and 2 CCTs) reported that acupuncture therapy was better than medication for the treatment of patients with RA (Luo et al., 2009). The discrepancies among these studies may be due to methodological quality such

as the low number of clinical trials and the small sample size of the included studies. On the other hand, the types of acupuncture and the control interventions used may affect the results. To derive a more precise estimation of the effect of acupuncture on RA, we performed an updated meta-analysis of all eligible studies.

In the present study, 21 RCTs containing 1772 patients were included. Through careful analysis, we demonstrated that acupuncture therapy appears to have more beneficial effect compared with non-acupuncture therapy for treating RA ($RR = 1.19$, 95% CI 1.08–1.31, $Z = 3.47$, $P = 0.001$). The similar results were found in the subgroup analysis of trials except the comparison of acupuncture vs. traditional Chinese drug. Furthermore, no serious adverse events resulting from acupuncture were reported.

Based on our results, acupuncture is beneficial for treating RA. However, due to the lack of standardized acupuncture treatment protocol, the applicability of evidence for the usefulness of acupuncture in RA was affected. For instance, the number of acupuncture points ranged from 2 to 31, the duration of needle insertion varied from 2 to 40 minutes, and the number of sessions ranged from 12 to 60. All of these factors including acupuncture points selected, frequency of stimulation, total number of sessions and intervention duration could have an impact on outcomes (Kim et al., 2011).

The acupuncture mechanism of action in the treatment of RA remains unclear. These mechanisms could be explained in terms of anti-inflammation, modulation of autonomic nervous system or analgesic effects of acupuncture in patients with RA (Lee et al., 2008). It is shown that multiple physiological pathways, including the hypothalamus-pituitary-adrenal (HPA) axis, sympathetic pathways and parasympathetic cholinergic pathway were involved in mediating the anti-inflammatory effects of acupuncture (McDonald et al., 2013). Some researchers have detected that acupuncture could regulate the balance between Th1 and Th2 cell-derived pro-inflammatory and anti-inflammatory cytokines (Liu et al., 1993; Xiao et al., 1992; Zhang et al., 2010). Increased serum level of interferon- γ (IFN- γ) and interleukin-2 (IL-2) were found in RA patients after acupuncture therapy, accompanied with decreased level of TNF- α . Furthermore, it is suggested that acupuncture combined with moxibustion has equivalent effect on analgesia compared with analgesics. This might correspond with the analgesic theories of acupuncture, which claim to reduce pain by stimulating the serotonergic, noradrenergic and opioid system. However, these theories regarding the mechanism of acupuncture are not fully established and need future research.

The present meta-analysis has several limitations that should be considered. First, of the 21 RCTs included, only one study was of high quality (Chen et al., 2012). Most of the studies did not give any details of the randomization method, blindness, description of drop-outs and withdrawals. Trials with inadequate blinding and inadequate allocation concealment are likely to show exaggerated treatment effects and thus limit the reliability of the study results. Second, no long-term study was included in the meta-analysis. Follow-up durations of the included trials ranged from 15 days to 6 months, and thus long-term follow-up studies are needed. Finally, all of the included RCTs were reported only in the Chinese literature, and studies from one country is known to exhibit a very low rate of negative results (Vickers et al., 1998).

In conclusion, this concise report of a systematic and meta-analysis approach demonstrates significant efficacy of acupuncture treatment vs. non-acupuncture treatment in improving the symptoms of RA. However, the total sample size and the methodological quality were too low to draw firm conclusions about the effectiveness of this approach. Thus, high quality repeatable multi-center randomized controlled trials with larger sample sizes are needed to strengthen our conclusion. In addition, more researches should be investigated to determine the role of acupuncture treatment in RA.

Conflict of Interest Statement: We have no conflicts of interest to declare.

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