Abstract: Patients with rheumatic diseases always try to look for "magic bullets" to cure their illnesses. Of all the available complementary and alternative medicine in Hong Kong, traditional Chinese medicine (TCM) is by far the most commonly adopted alternative. In this report, we present four case studies on patients with spondyloarthropathy; their medical histories and the different alternative therapies they adopted for their diseases. The four seemingly different herbal treatments turned out to be using similar ingredients/herbs (such as Tripterygium wilfordii Hook F [雷公藤]) contained in TCM drugs such as Tongbiling (通痹靈). We also review briefly the use of acupuncture, and some other herbal TCM in other rheumatic diseases. Finally, we discuss about the reasons why our patients use alternative therapies, and the issues which physicians should be aware of.

Keywords: Acupuncture, rheumatic diseases, spondyloarthropathy, traditional Chinese medicine

Introduction

Patients with rheumatic diseases always try to look for "magic bullets" to cure their illnesses. Although newer therapeutic agents are available compared with the past, there is no curative treatment so far. Hence, patients seek for complementary and alternative medicine. In Hong Kong, traditional Chinese medicine (TCM) is the most commonly adopted alternative.

In this article, we present four case studies on patients with spondyloarthropathy. Their medical histories and the different alternative therapies they adopted for their disease are described. Their different herbal treatments turned out to be using similar ingredients/herbs (such as Tripterygium wilfordii Hook F [雷公藤]) contained in TCM drugs such as Tongbiling (通痹靈). Studies on Tongbiling are reviewed. In addition, we discuss about the therapeutic mechanism of Tripterygium wilfordii Hook F, its use in other rheumatic diseases and its side effects.

Case Histories

Case 1

A 28-year-old woman presented with on and off ankle pain and swelling for 6 years in 2003. She was healthy and did not have any family history of arthritis or skin problem. Radiology of her SI joints was normal but MRI revealed tenosynovitis of both ankles. A diagnosis of spondyloarthropathy was made. Her inflammatory markers were elevated (ESR 37 mm/hr [NR <15 mmHg] and CRP 24 mg/L [NR <8 mg/L]). Sulphasalazine was started in December 2003 and methotrexate was added in January 2004. Due to the inadequate response and financial cost, anti-TNFα
therapy was discontinued after 6 doses. She was put on thalidomide in April 2005 but she discontinued the drug herself because of dizziness. Subsequently, she was lost to follow-up in our clinic and returned to us in September 2005. At that time, she informed us that she was put on herbal treatment from herbalists in Guangzhou. The herbal regime consisted of Tongbiling (通痹靈)/Tongbiheji (通痹合劑), Jixueteng (雞血藤), Nansheteng (oriental bittersweet) (南蛇藤) and some herbal tea preparation. In order to identify the specific ingredients contained in Tongbiling/Tongbiheji, we sent the medicine to the Chemical Pathology Laboratory in Princess Margaret Hospital for analytical testing. Part of the reply letter was quoted below:

"A bottle of 'Tongbi Heji' was received for chemical analysis. Triptophenolide, dehydroabietic acid, ethylparaben and unidentified substances were detected by HPLC-DAD and GC-MS. Triptolide and triptophenolide were detected by LC-MS/MS. Target analysis for steroids were negative. Triptolide (雷公藤素甲), triptophenolide (山海棠素) and dehydroabietic acid (去輕松香酸) can be found in Tripterygium wilfordii (雷公藤) and related plants. Tripterygium wilfordii (雷公藤) is used in Traditional Chinese Medicine for rheumatic diseases. Extracts of Tripterygium wilfordii is also used in modern Integrated Medicine for a wide range of autoimmune diseases. However, this herb is toxic and contraindicated in pregnancy..."

For the herbal tea preparation, information on the ingredients was obtained from a herbalist in the Central Health Protection Unit:

- 富歸，亦芍，川芎：養血補氣
- 白芍，生苡仁：去濕
- 澤瀉，澤蘭：消腫
- 南蛇藤，雞血藤：祛風濕，活血脈，消腫止痛

She responded to the herbal treatment with clinical improvement. The trend of her inflammatory markers is shown in Figure 1. In her last follow-up, she stopped the herbal tea but was still receiving Tongbiling and diclofenac. She did not experience early morning stiffness and the VAS pain and global health scores were both 3/10. Physical examination revealed mild left lateral malleolus swelling with minimal tenderness.

**Case 2**
A 33-year-old man initially presented with pain over sacroiliac joint, back and buttock pain for 2 years in 1999. Physical examination revealed bilateral sacroiliitis tenderness. He was diagnosed to have ankylosing spondylitis. Due to the elevated inflammatory markers and inflammatory back pain despite NSAID therapy, he was put on sulphasalazine in April 1999. Methotrexate was added in September 2001 because of persistently active disease. A trial of intravenous pamidronate was given in April 2002 in combination with

![Figure 1. Trend of inflammatory markers in case 1.](image-url)
methotrexate but this was not effective. Treatment was stopped because of inefficacy and deranged liver function. Treatment was then switched to leflunomide from April 2002 to July 2002, followed by oral cyclophosphamide. Obvious improvement in inflammatory markers was seen in the subsequent few months. On further enquiry, he disclosed that he was also on herbal therapy containing "Thunder god vine" (雷公藤). Our course of cyclophosphamide was stopped after 6 months but he continued the herbal tablets till July 2004. Figure 2 showed the trend of his inflammatory markers.

After the dosage reduction of his herbal tablets, his joint condition deteriorated. He finally agreed for anti-TNFα therapy. He is currently on maintenance anti-TNFα therapy and his disease is well controlled.

**Case 3**

A 64-year-old woman with a history of diabetes mellitus presented with polyarthralgia in 1998. A diagnosis of spondyloarthropathy was made in July 1998 and sulphasalazine was started. However, her drug compliance was not good. In 2001, she was found to have moderately differentiated adenocarcinoma arising from tubulovillous adenoma in a colonic polyp. There was no residual lesion after polypectomy. She had several trials of herbal therapy and acupuncture for her joint problem but the response was fair. In February 2004, intravenous pamidronate was started but this was not effective. She requested a trial of anti-TNFα therapy in April 2004 despite a recent history of malignancy. Clinical and biochemical improvement was noted. Unfortunately, she developed skin rash after 4 doses of infusion and she preferred to be put on herbal therapy from China again. Her disease flared in August 2004 and she was put on herbal syrup containing Tongbiling/Tongbiheji and herbs jixueteng and nansheteng. Drastic improvement was seen with subsidence of peripheral tenosynovitis. Treatment was stopped for 3 months in mid-2006 due to haematuria and restarted in August 2006 with progressive dosage reduction. Figure 3 showed the trend of her inflammatory markers.

**Case 4**

A 31-year-old electronic engineer had a history of right knee pain in 1992 and right anterior uveitis in 2001. He was subsequently diagnosed in QMH to have ankylosing spondylitis with sacroiliitis. NSAID was started and sulphasalazine was added in November 2001. Due to advanced left hip osteoarthritis, a total hip replacement was performed in June 2006. He was first seen in our clinic in December 2006 due to geographical reason. At that time, he was well with no early morning stiffness or pain. In subsequent follow up visits, he unveiled that he was on herbal treatment for about 1 year. The herbal tea included jixueteng, 甘草, 赤芍, 生苡仁 and 澤蘭. Tongbiling and tongbiheji were used as well. The trend of his inflammatory markers is shown in Figure 4.
Discussion

An increasing number of patients are using complementary and alternative medicine all over the world, which led the WHO to publish its Traditional Medicine Strategy in 2002-2005. The interest in TCM shows that patients are looking for alternative therapeutic options.

TCM is a comprehensive conceptual system that is very different from the approach of western medicine. It works in five solid organs – heart, liver, spleen, lung, and kidney – and six hollow viscera – large and small intestine, urinary bladder, stomach, gall bladder, and 'triple burners'. These 'structures' are connected by conduits and vessels with 'qi' (energy) and blood circulating through them. It is a concept of how the
body functions. The ‘qi’ and blood are vital substances of life; the function of the solid organs is to store these substances, and the hollow viscera act as reservoirs to regulate the circulation of these substances. TCM is a holistic approach which emphasizes the importance of keeping all the structures functioning harmoniously. Good health results when these structures in the body stay in harmony.

**Tongbiling (通痠靈)**

Various published studies have demonstrated beneficial effects of Tongbiling (TBL) on arthritis. In one study on Th1 type cytokine expression, it was shown that 200 mg/L and 100 mg/L TBL could inhibit interferon (IFN)-γ and TNF-α expression on T lymphocytes. In another study, the amount of monocyte chemoattractant protein-1 (MCP)-1 mRNA expression in synoviocytes from rats with adjuvant arthritis was distinctly decreased with TBL. Overall alkali TBL could significantly down-regulate CD69 expression on activated mouse T lymphocytes in a dose-dependent manner. Furthermore, it could inhibit significantly the synovial fibroblast proliferation, and down-regulated interleukine (IL)-1, TNF-α and PGE2 production. From the results of ingredient testing in our patients' herb teas, we know that Tongbiling contains the herb Tripterygium wilfordii Hook F.

**Tripterygium wilfordii Hook F (TWHf) (雷公藤)**

TWHf is the most commonly prescribed TCM in China for treating rheumatoid arthritis. Studies in laboratory animals have indicated that extracts of TWHf suppress both immune and inflammatory responses. It is also effective in treating a number of autoimmune diseases in animal models. Its immunosuppressive activity has been attributed to components such as triptolide, tripidiolide, tritonide and triptophenolide. The mechanisms of this herb include:

1. Inhibits pokweed mitogen (PWM) – stimulated IgM and IgG production from peripheral blood mononuclear cells;
2. Decreases IL-1 production by monocytes stimulated with zymosan;
3. Suppresses the production of monokines such as TNF-α, IL-6 and IL-8, and lymphokines, IL-4 and IL-10;
4. Inhibits PGE2 synthase in lipopolysaccharide-stimulated human monocytes and fibroblasts from rheumatoid arthritis synovial tissue;
5. Inhibits T-cell IL-2 production with higher potency than prednisolone and cyclophosphamide;
6. Decreases the amount of soluble E-selectin, ICAM-1 and vascular cellular adhesion molecule-1 expressed by human neutrophils, synovial fibroblasts and endothelial cells.

TWHf has also been extensively used in China to treat systemic lupus erythematosus (SLE). It was shown that in conjunction with steroids, it may induce remission in patients with severe lupus nephritis.

A phase I study of the ethyl acetate (EA) extract of TWHf in 13 patients with rheumatoid arthritis (RA) showed that TWHf is safe in dosages of 570 mg/day. Improvement was defined by the American College of Rheumatology response criteria (ACR 20), as well as a change in ESR and CRP. Three patients withdrew as they did not experience improvement. Six of the 10 remaining patients treated with 180 mg/day EA showed disease improvement. Eight of the 9 patients, who received doses greater than 360 mg/day, experienced both clinical and laboratory improvement. One patient met the ACR criteria for remission.

A prospective, double-blind, placebo-controlled 20-week study in 35 patients with long-standing, refractory, RA was performed to evaluate the efficacy of TWHf. Patients were randomly assigned to placebo, low-dose (180 mg/day), or high-dose (360 mg/day) EA extract. The high-dose group showed ACR 20 improvements when compared with the placebo group (P=0.0001). The effectiveness shown by the low-dose group was greater than that of the placebo group (P=0.0287); but was less than that of the high-dose group (P=0.027).

Despite its impressive therapeutic effect, its side effects should not be ignored. It has gynecological, gastrointestinal and haematological adverse effects. It may cause reversible amenorrhea (younger than 40 years old and less than 2 years of amenorrhea) and vaginal spotting. Common gastrointestinal upsets include diarrhoea, nausea, vomiting, and dryness of mouth, angular stomatitis, oral ulcers, gastritis and abdominal pain. Leukopenia, thrombocytopenia, deterioration in bone mineral density, diastolic hypertension, hair loss, rash, skin pigmentation and headaches are other possible side effects.
Other TCM and Herbs

Celastrus orbiculatus, isolated from aerial parts of Celastrus orbiculatus thunb, is an inhibitor of cyclooxygenase COX 2 activity of prostaglandin H2 synthase. It was identified as (-)-epiafzelechin, a member of flavan-3-ols, which was dose-dependent. (-)-epiafzelechin exhibited about 3-fold weaker inhibitory potency on the enzyme activity than indomethacin as a positive control. It was shown to exhibit significant anti-inflammatory activity on carrageenin-induced mouse paw oedema.

Harpagophytum procumbnes, common name known as Devil's claw, was used in traditional southern African medical therapies for arthritis, low back pain, neuralgia, headaches and to reduce fever. The leading compound of such extracts, harpagoside, has anti-inflammatory effects due to its action on eicosanoid biosynthesis. Another extract WS1531, was shown to reduce production of myeloperoxidase from stimulated neutrophils and may block the prostaglandin E2 inflammatory pathway by inhibiting cyclooxygenase-2 activity. In a double-blind, randomised 4-week study comparing 2 daily doses of WS1531 with placebo in 197 patients who were prone to chronic lower back pain, significant effect was seen in the treatment group, though the number of responders was small.

Salix spp., willow tree, is regarded as one of the first examples of a modern drug developed from herbal remedy. The analgesic and anti-pyretic properties of willow bark have been known since the ancient Egyptian, Greek, Indian and Roman civilisations. The oxidation of salicin, a constituent of willow bark, yields salicylic acid, while the major metabolites also include gentisic acid and salicyuric acid. A 4-week randomised double-blind study evaluated the efficacy of willow bark extract in 210 patients with current exacerbations of chronic lower back pain. The principal outcome measured was the number of patients who were pain-free and did not use any tramadol for at least 5 days in the last week of the study. Thirty-nine percent in the high-dose group (240 mg salicin), 21% in the low-dose group (120 mg salicin) and 6% of those receiving placebo achieved this end-point, this difference is statistically significant.

In Hong Kong, a study to investigate the supplementary treatment efficacy for RA by capsules of the following TCM groups vs. placebo groups was carried out:

- Lingzhi (Ganoderma lucidum), and
- San-Miao-San (Rhizoma atractylodis, Cortex phellodendri, Cortex phellodendri bidentatae)

It was found that there was no significant difference in terms of the absolute counts, percentages, and ratios of CD4(+) / CD8(+) / natural killer/B lymphocytes between the TCM and the placebo groups.

It was found that after taking the capsules/placebos for 8 and 24 weeks, there were no significant changes in the concentrations of:
1. plasma cytokines of interferon-γ-induced protein-10;
2. MCP-1;
3. monokine induced by interferon-γ, regulated upon activation normal T-cell expressed and secreted; and
4. interleukin (IL)-8, and IL-18.

It was found that after taking the capsules for 24 weeks, the percentage changes in ex vivo-induced level of inflammatory cytokine IL-18 was significantly lower in the TCM group than in the placebo group.

Within the limits of this study, it was concluded that Lingzhi and San-Miao-San capsules might exert a beneficial immunomodulatory effect in patients with rheumatoid arthritis.

Acupuncture

In 1986, a double blind crossover study of 10 ankylosing spondylitis patients with persistent pain and stiffness, was conducted by Professor Paul Emery in Leeds, United Kingdom. Six of them were taking anti-inflammatory drugs. Needles were inserted into standard acupuncture points in the treatment group of patients. High and low frequency current supplied for 20 minutes in treatment group while sham procedure involved the application of needles to the same sites causing a prick but without entering the skin was given to the control group. Each treatment session lasted for 20 minutes and each patient received either three active or three sham treatments over a 3-week period. This was followed by a 3-week washout interval and then crossover to the opposite arm for treatment. Spinal movement, chest expansion and visual analog scales for pain and stiffness were examined. Objective measurement, which was altered by 10%, was considered significant at the end of the study. No significant effect of either active or dummy treatment on pain...
was shown. However, stiffness was significantly improved (p<0.01). There was marginally significant improvement of neck movement with active treatment.

The overall conclusion was that acupuncture had very little value in the control of pain in patients with ankylosing spondylitis.

Furthermore, the small sample size and short treatment period in this study may severely undermine the claim of the usefulness of acupuncture in these chronic illnesses.

In various independent studies in China, acupuncture has been shown to have beneficial effects in patients with spondyloarthropathy. Unfortunately, those details are not available.

A review from Germany which examined 17 studies about the efficacy and scientific quality of acupuncture in rheumatoid arthritis; spondyloarthropathy; systemic lupus erythematosus; limited and systemic scleroderma found that acupuncture failed to meet sufficiently good quality in most of the studies. Hence, the author suggested that acupuncture could not be recommended for treatment of these diseases.

For the effectiveness of acupuncture in peripheral joint osteoarthritis, a systemic review and meta-analysis was conducted by Kwon et al. Trials assessing needle acupuncture with or without electrical stimulation were considered if sham- or placebo-controlled or controlled against a comparator intervention. Thirty-one possibly relevant studies were identified and 18 randomised-control trials were included. Ten trials tested manual acupuncture and eight trials tested electro-acupuncture. Overall, these ten studies demonstrated greater pain reduction in acupuncture groups as compared with the controls. The meta-analysis of homogeneous data showed a significant effect of manual acupuncture compared with the sham acupuncture. Considering its favourable safety profile, acupuncture seems to be an option worthy of consideration, particularly for knee osteoarthritis.

What Are the Probable Problems Associated with the Use of Alternative Medicine?

Since traditional Chinese medicines are derivatives of natural products that have been in use for centuries in China, the lay public believes they are safe to use. Moreover, people like to seek alternative treatments that are more congruent with their own values, beliefs, cultural inheritance, and philosophical orientations toward health and life. With an increased interest in disease prevention, many people focus their attention on fitness and stress management with a view to have controls on their own illnesses, and hence lessen their dependence on the physicians.

However, in real life it is not this simple. The probable problems associated with alternative therapies such as TCM are as follows:

1. Guidance to health-care providers in retrieving information from patients concerning their TCM therapies is often limited, this is because of:
   (i) lack of familiarity of the providers with these compounds, and
   (ii) lack of scientifically verified data.

2. Clinical researches on most of the TCM therapies have not been done, and for those few that were done, a centralized database is not available to store the findings and results of these studies.

3. Adverse herb-drug interactions may occur when TCM, prescription drugs and/or over-the-counter medications are in concomitant use. This is especially true in the elderly who are more likely to be using multiple drugs.

4. Furthermore, herbal compounds may not fully enlist all of the active ingredients, and hence may lead to potential adverse effects.

With a different conceptual system and therapeutic mechanism, one has to realise that efficacy of the herb-derived preparations can be affected by:

- the extraction procedure utilised;
- the dosage used;
- the duration of treatment, and
- the route of administration.

Efficacy of the botanical may be due to synergistic action of several compounds together, or due to a balance of synergist and antagonist actions between these compounds. Hence, the testing of a single compound may not be a fair evaluation of the efficacy of the "crude" extracts used by patients.

Conclusion

Despite newer therapeutic options for patients with rheumatic diseases in this era, TCM and acupuncture remain as popular alternative therapies. It is important for the health care
providers to monitor for adverse reactions if the patients are adopting such therapies. Discussion of the pros and cons of these treatments is useful for patients' rational decision.

References