MONITORING OF LIVER ENZYMES IN PATIENTS ON CHINESE MEDICINE

by Mazin Al-Khafaji

Background

The status of TCM in Britain and across Europe is still precarious and uncertain. One of the primary areas of vulnerability is the issue of safety. Herbal combinations are highly complex products with dozens of active ingredients that can have a profound effect on the physiology of the body. It is not surprising that some patients are susceptible to adverse reactions at times. Over the past decade there have been several highly publicised cases of patients developing idiosyncratic toxic hepatitis following a course of Chinese herbs. Although most such cases recovered without incident, there have been a number of tragic cases where death was the outcome.

Since it is now well established that toxic reactions do occur, it is of the utmost importance that we determine the incidence of such reactions. Failure on our part to take the initiative and establish protocols for testing would expose us to increasingly fiercer attacks, and rightly so.

To maximise safety, and begin to amass data on the incidence of adverse reactions, between October 1996 and August 1999, a period of 33 months, all patients attending my clinic for Chinese herbs had to undergo a blood test to check levels of alanine aminotransferase ALT (previously known as glutamic-pyruvic transaminase GPT) at regular intervals.

Design

All patients had blood tests to check ALT levels at the following intervals: before commencement of treatment, after 3 weeks and then every 10 weeks of treatment thereafter until discontinuation of treatment. If patients reported any adverse reaction that seemed relevant as a toxic or idiosyncratic response to the Chinese herbs, or if the prescription of herbs was dramatically altered, another blood test was performed.

All blood samples were analysed at the clinic using a Refletron blood testing machine that was calibrated and checked every 3 months for correct functioning.

Of the variety of liver parameters that could have been checked, ALT was chosen because most authorities agree that, along with alkaline phosphatase, it gives the best indication of how the liver is coping with metabolising medication. Alkaline phosphatase was not used because strips require special storage facilities, which is not the case with ALT strips.

All patients who had completed at least 5 weeks of treatment with Chinese herbs were included in this assessment. All patients were prescribed raw herbs that were decocted by them at home and consumed daily (in two doses). An average formula would contain approximately 1.5-2g per kilogram weight of patient. So for example a child weighing 25kg received a formula containing between 37-50g of raw herbs per day, an adult weighting 70g received 90-120g.

It was clear to me after a short period of time that a significant percentage of patients developed slightly elevated ALT levels (male >42, female >32) soon after starting treatment with Chinese herbs. After consultation I decided that any patient who developed raised ALT readings would continue with treatment as long as the readings did not exceed 3 times the upper limit of normal (3x ULN). Patients with raised ALT readings had to undergo further blood tests at intervals of 7-14 days to monitor the liver, until either the readings returned to normal or exceeded 3x ULN. Any patient with raised ALT levels above 3x ULN would have to discontinue treatment.

Patients

The total number of patients who had at least 5 weeks of treatment, and therefore at least 2 blood tests was 1265. Of those 821 (65%) were female and 444 (35%) were male. 94 (about 7.5%) were children below the age of 11. The youngest patient was 6 months, the oldest 92. The mean age was 37.3 years. 772 cases (61%) received between 5 and 13 weeks of treatment; 398 cases (31.5%) received between 13 and 23 weeks of treatment; 95 cases (7.5%) received over 23 weeks of treatment. Table 1 outlines the disease or the type of disorder (with the percentage of total) that the patients suffered from.

Disorder	No. of cases	Approximate %
Atopic dermatitis	215	17
Eczema[1]	184	14.5
Psoriasis	177	14
Acne & rosacea	162	12.8
Other skin disorders	103	8.1
Digestive disorders	77	6.1
Gynaecological disorders	75	5.9
Auto-immune disorders	75	5.9
Rheumatic disorders	57	4.5
Respiratory disorders	52	4.1
Other disorders	88	7

Results

Of the 1265 patients, a total of 124 cases (9.8%) had raised ALT levels before commencement of treatment . In all cases ALT levels were below 3x ULN, and so treatment was administered. Of these patients 71 cases (57.3%) had normal readings by the time they stopped treatment, 48 cases (38.7%) had no significant change of ALT levels, and 5 cases (4%) discontinued treatment before a third reading was taken (which is when the majority showed improvement in ALT levels). See table 2.

Table 2. Raised ALT levels before commencement of treatment

	Male	Female	Total	% of all patients
Raised before treatment	58 (13.1%)	66 (8%)	124	9.8%
Remained raised	24 (44.4%)	24 (36.9%)	48 (38.7%)	3.8%
Returned to normal	30 (55.6%)	41 (62%)	71 (57.3%)	5.6%
Did not continue treatment after 2nd reading	4 (3.2%)	1 (0.8%)	5 (4%)	0.4%

A total of 107 cases (8.46%) developed raised ALT readings after initially having normal readings (see table 3). 9 cases discontinued treatment of their own volition, and not because their readings exceeded 3 times normal. In 94 cases (94.9% of patients who developed abnormal readings and continued treatment) ALT levels returned to normal with no further incident. Of these patients about 25-30% reported some degree (usually mild) of abdominal discomfort, looseness of bowels, loss of appetite or fatigue. In 4 cases (4.1% of patients who developed abnormal readings and continued treatment, which is 0.4% of total sample), ALT readings did not return to normal. Of these, 2 were male and 2 female. None of the patients whose readings did not return to normal had a previous history of liver disease. I shall discuss each in turn.

Patient 1, male age 44, psoriasis

His initial reading was on the upper limit of normal at 39.6U/l (normal range for male is > 42U/l). After 3 weeks of treatment his reading reached 82.6U/l. Treatment continued for a further 6 weeks with blood tests performed every two weeks. ALT readings never exceeded double normal levels (70.9, 79.5 and 60.8 U/l respectively) nor did the patient report any adverse reaction. Treatment was discontinued after a total of 9 weeks due to poor response and continued elevation of ALT levels.

The prescription he was on until week 3 was as follows:
Sheng Di Huang (Radix Rehmanniae Glutinosae) 30g
Tu Fu Ling (Rhizoma Smilacis Glabrae) 30g
Mu Dan Pi (Cortex Moutan Radicis) 9g
Huai Hua (Flos Sophorae Japonicae Immaturus) 15g
Chi Shao (Radix Paeoniae Rubrae) 9g
Ban Lan Gen (Radix Isatidis seu Baphicacanthi) 12g
Cao He Che (Rhizoma Polygoni Bistortae) 12g
Da Qing Ye (Folium Daqingye) 12g
Shan Dou Gen (Radix Sophorae Subprostratae) 9g
Gan Cao (Radix Glycyrrhizae Uralensis) 6g

Between week 3 and week 5, Shan Dou Gen was removed, otherwise the prescription was unaltered. For the remaining 4 weeks he was on the following prescription:
Sheng Di Huang (Radix Rehmanniae Glutinosae) 30g
Bai Hua She She Cao (Herba Oldenlandiae Diffusae) 30g
Mu Dan Pi (Cortex Moutan Radicis) 9g
Zi Cao (Radix Lithospermi seu Arnebiae) 12g
Chi Shao (Radix Paeoniae Rubrae) 9g
Ban Lan Gen (Radix Isatidis seu Baphicacanthi) 12g
Jin Yin Hua (Flos Lonicerae Japonicae) 12g
Da Qing Ye (Folium Daqingye) 12g
Gan Cao (Radix Glycyrrhizae Uralensis) 6g

Patient 2, male age 46, psoriatic arthritis

Salazopyrine 2.5g/day. Piroxicam 20 mg/day.
Initial reading was 28.9 U/l; after 3 weeks of treatment his reading was still normal at 22.4 U/l. By week 13 he developed a reading of 85.5U/l, about double normal levels, but reported no ill effects. At week 15, ALT reading was still elevated at 66.7 U/l. The patient discontinued treatment due to limited response.The primary prescription used was as follows:
Sheng Di Huang (Radix Rehmanniae Glutinosae) 30g
Ji Xue Teng (Radix et Caulis Jixueteng) 30g
Ren Dong Teng (Caulis Lonicerae) 30g
Qin Jiao (Radix Gentianae Macrophyllae) 12g
Di Long (Lumbricus) 9g
Wei Ling Xian (Radix Clemetidis Chinensis) 12g
Tu Fu Ling (Rhizoma Smilacis Glabrae) 30g
Mu Dan Pi (Cortex Moutan Radicis) 9g

Chi Shao (Radix Paeoniae Rubrae) 9g
Fang Feng (Radix Ledebouriellae Sesloidis) 9g
Sang Zhi (Ramulus Mori Albae) 12g
Gan Cao (Radix Glycyrrhizae Uralensis) 6g

The only modification between week 13 and 15 was the removal of Sang Zhi and the addition of Hong Teng (Caulis Sargentodoxae Cuneatae) 15g, and Hai Feng Teng (Caulis Piperis) 12g.

Patient 3, female age 28 years, post adolescent female acne

She was not taking any other medication. ALT readings were normal at commencement of treatment (18.7 U/l) and at week three (24.9 U/l), but had risen to 103 U/l at week 13, which is 3x ULN. She complained of fatigue but no other symptoms. Her appetite and bowels were normal. She discontinued treatment for two weeks and then resumed once again. After a further 2 blood tests 2 and 4 weeks later, her readings reduced to double normal (58.6 and 51.5 U/l respectively). She continued to feel tired though this became less pronounced. The prescription she was on at the time of elevation was as follows:

Bai Hua She She Cao (Herba Oldenlandiae Diffusae) 20g
Dang Gui (Radix Angelicae Sinensis) 9g
Hong Hua (Flos Carthami Tinctorii) 9g
Tao Ren (Semen Persicae) 9g
Chi Shao (Radix Paeoniae Rubrae) 9g
Gan Cao (Radix Glycyrrhizae Uralensis) 6g
E Zhu (Rhizoma Curcumae Zedoariae) 9g
Yi Mu Cao (Herba Leonuri Heterophylli) 12g
Lian Qiao (Fructus Forsythiae Suspensae) 12g
Zhi Ke (Fructus Citri seu Ponciri) 9g
Huang Qin (Radix Scutellariae Baicalensis) 9g

Between week 15 and 17 no changes were made to the prescription. Despite this, ALT readings remained below twice normal levels. At this stage treatment was discontinued due to satisfactory improvement with acne.

Patient 4, female, age 64 years, generalised and non-specific pruritis

This patient had the most dramatic change in ALT levels after an initial normal reading (24.2 U/l) before commencement of treatment. On week one, she complained of slight looseness of bowels. On week three she complained of increasing itching but no other symptoms. On checking the liver at week 3, her ALT levels were found to have risen to 1210 (almost 38x ULN). Treatment was immediately discontinued. Within the next 48 hours she developed great fatigue and jaundice. She has undergone full investigation by an gastroenterologist and the conclusion is that it is highly probable that she had suffered from an idiosyncratic liver toxicity due to Chinese herbs. Since then she has made a full recovery. The prescription and doses were as follows:

Sheng Di Huang (Radix Rehmanniae Glutinosae) 15g
Chi Shao (Radix Paeoniae Rubrae) 9g
Mu Dan Pi (Cortex Moutan Radicis) 9g
Bai Ji Li (Fructus Tribuli Terrestris) 12g
Sheng Ma (Rhizoma Cimicifugae) 6g
Mu Tong (Caulis Mutong) 6g
Dan Zhu Ye (Herba Lopthatheri Gracili) 9g
Zhi Mu (Radix Anemarrhenae Asphodeloidis) 9g
Gan Cao (Radix Glycyrrhizae Uralensis) 6g

On reporting looseness of bowels, the following modification was made: Sheng Di Huang was reduced to 12g with addition of 20g of Ge Gen (Radix Puerariae). She was given a further 12 days of the altered formula. One week later she phoned the clinic and complained that the itching had got worse, although her bowels were normal, so Fang Feng (Radix Ledebouriellae Sesloidis) 9g, was add to the remaining bags that she had.

Of the 107 cases who developed raised levels of ALT with treatment, 10 cases (9.36% of those who developed raised ALT with treatment, which is 0.79% of the patients in the total sample) had readings that exceeded 3x ULN (= 126U/l in males and 96U/l in females) and consequently had to discontinue treatment at least for a period of time. However in 8 of those cases, it seems highly likely that other factors aside from the Chinese herbs played a significant role.

Four males (2 suffering with psoriatic arthritis and 2 with gout) had readings that slightly exceeded 3 times normal levels. In all 4 cases the patients had consumed large doses of pain killers and/or NSAI in the days leading to the blood tests. All 4 discontinued treatment for 2 weeks and then resumed treatment. None showed abnormal readings after this, despite being prescribed similar Chinese herbs.

Six females developed ALT levels that exceeded 3 times normal levels. 3 cases had consumed pain killers prior to the blood test (one for wisdom teeth extraction, 2 for dysmenorrhoea) and one had developed gallstones and cholecystitis. All 3 women who had taken pain killers had normal ALT readings on re-commencement of treatment after 2 weeks without herbs. The women who developed gallstones and cholecystitis did not continue treatment with Chinese herbs. The remaining two females who had readings that exceeded 3 times normal levels, were also amongst the 4 cases that had persistently raised ALT levels with treatment (see previous section).

Table 3 Raised ALT readings following commencement of treatment:

	Male (45*)	Female (53*)	Total (98*)	% of total
Raised with treatment	46 (10.4% of males)	61 (7.4% of females)	107	8.46
Remained raised	2 (4.4%)	2 (5.66%)	4 (4.1%)	0.32%
Returned to normal	43 (95.6%)	51 (94.34%)	94 (95.9%)	7.43%
Ceased treatment before 3rd blood test	1 (2.2%)	8 (13.11%)	9 (8.4%)	0.71%

* figures show no. of patients who completed at least 3 blood tests

It is of considerable interest to group the patients who had raised ALT levels with treatment according to the stage of treatment that they were at when they developed it (see Table 4).

• 83 cases (77.6%) of the patients who developed raised readings developed them on week 3 of treatment, this is 6.6% of the patients still on the treatment.

• 22 cases (20.5%) developed raised readings on week 13, this is 5.5% of the patients still on the treatment.

• 2 cases (1.9%) developed raised readings on week 23 of treatment, this is 2.1% of the patients still on the treatment.

Table 4. Stage of treatment when ALT levels exceeded normal.

Week	Male (% of all males with raised ALT)	Female (% of all females with raised ALT)	Total & % of patients with raised ALT	Total & % of patients still on treatment	% of patients with raised ALT in relation to those still on treatment
1-3	38 (82.6%)	45 (73.8%)	83 (77.6%)	1265 (100%)	6.6%
3-13	7 (15.2%)	15 (24.6%)	22 (20.5%)	398 (31%)	5.5%
13-23	1 (2.2%)	1 (1.6%)	2 (1.9%)	95 (7.5%)	2.1%

It is also rewarding to group the patients who had raised ALT levels according to the primary condition they suffered from (see table 5). It should be noted that aside from psoriasis, atopic dermatitis, eczema and acne, I felt that there were insufficient numbers to draw accurate conclusions about other conditions. 23.7% of the psoriasis patients developed some abnormality with treatment. Aside from psoriasis, there is a roughly equal percentage of patients (6.5% for atopic dermatitis, 5.4% for eczema, and 4.9% for acne and rosacea) that developed raised ALT levels with treatment.

Summary

• 66.5% of patients suffered with skin disorders.

• 9.8% of patients had raised ALT readings before commencement of treatment.

• 8.46% of patients developed raised ALT with treatment.

• 95.9% of those who developed raised ALT readings returned to normal; whilst 4.1% remained raised.

• Only 25-30% of patients who developed raised readings reported symptoms (mostly digestive disturbance including anorexia, discomfort and bloating of the abdomen, fatigue and loose stools or diarrhoea).

• 9.4% of those who developed raised ALT with treatment; (0.79% of the patients in the total sample) had readings that exceeded 3x ULN. 80% of those were almost certainly due to other factors, primarily other medication they had taken in the days leading to the blood test.

• According to this limited investigation of 1265 cases, we can say that 1 in 1265 patients may develop toxic hepatitis.

Table 5. Conditions associated with raised ALT

Condition	Male (% of all males with raised ALT)	Female (% of all females with raised ALT)	Total (%) of those with raised ALT	% of total no. of patients with that condition
Psoriasis[2]	30 (65.2%)	12 (19.7%)	42 (39.25%)	23.7%
Atopic dermatitis	6 (13%)	8 (13/1%)	14 (13.1%)	6.5%
Eczema	2 (4.35%)	8 (13.1%)	10 (9.3%)	5.4%
Acne/ rosacea	3 (6.5%)	5 (8.2%)	8 (7.5%)	4.9%
Asthma	1 (2.2%)	4 (6.6%)	5 (4.7%)	-
Anxiety/ insomnia		3 (4.9%)	3 (2.8%)	
Prurigo nodularis	1 (2.2%)	2 (3.3%)	3 (2.8%)	
Hypertension		2 (3.3%)	2 (1.9%)	
Lichen planus		2 (3.3%)	2 (1.9%)	
Lichen simplex		2 (3.3%)	2 (1.9%)	
Uterine bleeding		2 (3.3%)	2 (1.9%)	
Gout	2 (4.35%)		2 (1.9%)	
IBS		1 (1.6%)	1 (0.94%)	
Graves disease		1 (1.6%)	1 (0.94%)	
Plane warts		1 (1.6%)	1 (0.94%)	
Pityriasis rosea		1 (1.6%)	1 (0.94%)	
Hepatitis C		1 (1.6%)	1 (0.94%)	
Chronic fatigue syndrome	1 (2.2%)		1 (0.94%)	
Rheumatoid arthritis		1 (1.6%)	1 (0.94%)	
SLE		1 (1.6%)	1 (0.94%)	
Pruritis (non-specific)		1 (1.6%)	1 (0.94%)	
Thrush		1 (1.6%)	1 (0.94%)	
Cervical spondylosis		1 (1.6%)	1 (0.94%)	
Vitiligo		1 (1.6%)	1 (0.94%)	

In this sample of 1265 cases monitored for changes in ALT levels whilst on Chinese medicine, 66.5% were treated for

disorders of skin. 8.46% of the patients developed abnormal levels of ALT whilst on the medicine, although the vast majority of these had only minor elevation (no more than 2x ULN). Much more work needs to be done in this area, but it seems highly likely that brief, minor elevation following commencement of treatment is of little significance since the majority (95.9%) returned to normal fairly rapidly (by the next time they were tested, i.e. 2 weeks) with no adverse symptoms or signs. It is probable that these transient changes are no more than an adaptive response by the liver to the initial introduction of the Chinese medicine.

The occurrence of raised ALT enzymes relative to the duration of time the patient was on treatment is of particular interest. This seemed to occur uniformly until week 23, when the incidence seemed to drop. So 6.6% of the patients still on the treatment developed raised ALT readings between week 1-3; whilst a similar percentage of 5.5% developed elevated levels between week 3-13. Between week 13-23 the incidence dropped to 2.1% of patients still on the treatment. This may well be an artefact due to the relatively low number of patients (95 patients, which is only 7.5% of the total sample) still on the treatment. These figures imply that if regular checks were made, then there is no merit in targeting any particular phase of treatment, when it would be more likely that patients will develop abnormal readings (certainly up until week 13).

Patients suffering with psoriasis were the most prone to develop raised readings whilst on Chinese medicine. Almost 1 in 4 had some abnormal elevation. In the vast majority of cases this was no more dramatic than 2x ULN, with a quick return to normal on subsequent testing. This may well be due to both the nature of the ingredients that are typically used for the treatment of psoriasis as well as to the fact that there is a significant percentage of psoriasis patients who have been shown to have abnormal liver architecture and fatty deposits[3]. If we looked at other disorders where sufficient data was available, it seems that approximately 5-6.5% developed transient ALT elevation.

Only 10 cases (0.79% of the patients in the total sample, and 9.36% of those who developed raised ALT with treatment) had readings that exceeded 3x ULN. However in 7 cases (70%), the patients had recently consumed pain killers or NSAID. On re-testing a few weeks later, ALT levels returned to normal despite the fact the patients resumed the Chinese medicine. The implication here is that either the herbs had no part to play in the raised enzymes or else they acted in concert with the drugs to do so. Much more work needs to be done in the area of interaction of biomedical drugs and Chinese herbs.

The advantages of regularly monitoring patients on Chinese herbs are indisputable. Not only will it be far more likely that the significant minority of patients who react adversely will be recognised earlier, and potentially serious consequences averted; it is possible in some cases to ascertain which individual ingredient has been responsible for the elevation. On several occasions, by regularly rechecking ALT levels and introducing one new ingredient at a time, it has been possible to discover which single ingredient or in some cases several ingredients the patient was intolerant to. By avoiding those ingredients, treatment could proceed with normal ALT readings and no ill effects.

The question of whether it is necessary to monitor every patient undergoing treatment with Chinese medicine is as crucial today as it was when it was first broached several years ago. The data collected here using 1265 patients is clearly insufficient to give an unequivocal answer; much work still needs to be done in this area to come to firm conclusions. In my opinion it seems highly probable that Chinese herbal medicine will prove to be a relatively safe form of treatment, and the risk benefit ratio would justify the rare cases of adverse reaction. However if we accept, as we must, that toxic reactions do occur, then clearly it is incumbent upon us, ethically, morally, and professionally to discover as soon as possible the incidence of such reactions. Anything short of this has to be considered a failing, which we can ill afford. TCM in this country is in its infancy and we must actively pursue (and be seen to be doing so) all avenues to discover and reduce any risk involved in taking Chinese medicine.

There is only one way that can finally give us the data we so badly need, and that is to monitor a sufficient number of patients that are undergoing treatment with Chinese herbs. We need to have in place a process that in time will generate meaningful data as to the frequency and severity of adverse reactions.

Notes

1 Includes seborrhoeic, pompholyx, discoid, asteototic, and stasis eczema.

2 Includes 4 cases that also suffered with psoriatic arthritis.

3 Zachariae H. Psoriasis and the liver. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1985: 47-64.

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