

## Interviews with Doctors

Dr. Min Yang

Q: How is current clinical treatment against tophi?

A: The biggest problem is that patients stop taking medications when they no longer feel pains.

Q: Are there serious conditions that drug treatment becomes ineffective and the patient cannot be treated?

A: Rarely. Most patients get their uric acid controlled as long as they keep taking medications as prescribed. The biggest problem is that patients stop seeing doctors during their treatment. When one medication does not take effect, we can increase the dose or combine different drugs, and the problem can usually be solved.

Q: What are the drugs that are commonly used for treatment?

A: Only 3: Allopurinol, Benzbromarone, and Febuxostat.

Q: Do they cause any adverse drug reactions?

A: Seldom. Allopurinol can cause allergy, but this is very unlikely to happen.

Q: Are patients self-disciplined in diet and taking medications?

A: Really not.

Q: Are patients with hyperuricemia but no obvious symptoms recommended to take medications?

A: Depending on the doctors' attitude. On one hand, the clinical practice guidelines are very strict, and since long-term high level of uric acid is harmful to the body, medications should be used; on the other, since there is no symptom, it is unlikely to make patients take medications for a long time. In principle, medications should be use when diet control is of little effect, but clinically after vain diet control we apply soda or let patients drink more water, then consider medications. Currently there are more young patients, and lifetime medication adherence is difficult for them.

Q: What do you think of our treatment in the intestinal tract?

A: I think it's good.

Q: What do you think of our treatment with dialysis?

A: Current medicines are enough to use, and maybe the patient group you are currently targeting is too small, for this kind of disease is rare. But your project has its own value, for the small group of patients do exist.

(Some Putian hospitals (unqualified private hospitals in China) recommended immunotherapy to lower uric acid level)

Dr. Beibei Cui

Q: How is current clinical treatment against tophi?

A: The absorption of gout may not be good. There can be localized ruptures, pus and infections during treatment, which causes problems of the whole foot/hand, and the patient may have to have an amputation if anti-infection treatment is not effective.

Q: Now that drugs can effectively treat tophi, why can there be such serious problems?

A: Patients have poor understanding of gout so their treatment starts late. Some patients had damaged kidneys, not to mention uric acid excretion, so the effect of medications may not be obvious; some patients had grown too many tophi for the body to absorb, making treatment very difficult. To make matters worse, the number of young patients is increasing.

Q: What do you think of our treatment in the intestinal tract?

A: That sounds good. You may bring this approach not only for patients with high uric acid disease, but also for joint treatment in patients with gout. But as only a third excretion of uric acid is in intestine, the purpose and effect of your treatment remain to be tested. For a long time we have ignored the effect of intestines in the excretion of uric acid. For the introduction of your project background you may stress the importance of the intestine. The points you may want to mention are: why do some patients have poor reactions on repeated blood uric acid lowering treatment? For some patients have renal dysfunction (uric acid crystals blocked their ureters) and the main route of uric acid excretion is through the intestinal tract.

Q: What do you think of our treatment with dialysis?

A: It's too much over the problem. Poor feasibility of usability. You'd better focus on the intestinal tract. Uric acid level is higher in joints than in blood, and dialysis can only target the blood, but the tophi in joints may not dissolve in blood is timely, so the efficiency can be a problem. Maybe local use? And hemodynamic issues (for immune absorption only the needles with the largest size or vein detained needles are used)? Also note the problem of hypouricemia.

Dr. Hua Zhao

Q: What are the problems you met in current clinical treatment against tophi?

A: The treatment lasts long (in years), and the patient's patience and compliance are not satisfactory (the compliance of gout patients is the worst in the rheumatoid immunology department); during treatment their uric acid level may fluctuate, causing them to lose confidence; acute gout can be possible; the drug treatment is continuously adjusted, but the patients may not pay return visits on time, leading to the irregularity use of medications; and their poor lifestyle factors like water intake.

Except for those with renal insufficiency, most patients can be cured with existing drug therapy, but there is still a prospect for dialysis programs for patients with chronic renal insufficiency.

Q: Why is gout so hard to treat?

A: Patients' poor compliance (the most important reason); people's lack of knowledge in gout;

the unprofessional treatment of doctors at grassroots clinics; the poor cooperation between doctors and patients and lack of regular return visits, etc. Frankly speaking, the treatment of gout is not very good now; the type of drugs is limited and there are not enough treatment methods.

Q: Are patients with hyperuricemia but no obvious symptoms recommended to take medications?

A: It depends. If the problem is controlled by diet and change of life styles then they do not need medications; if not, then medications are necessary.

Q: What do you think of our treatment in the intestinal tract?

A: I see a good prospect! Consider changing the intestinal microenvironment (especially pH) to create an environment in which uric acid dissolves and metabolizes more easily.

Q: What do you think of our treatment with dialysis?

A: Exchange efficiency? Hemodynamics? Blood clotting? There are many feasibility problems. Uric acid first becomes urate and then forms tophi, so consider the metabolic efficiency of urate to see whether you can effectively remove the urate in blood in time, and promote tophi dissolution. Another suggestion is that you can create an environment conducive to the tophi's dissolution at the exchange area to promote bacteria metabolism of urate. Maybe you should have more in-depth understanding of the background knowledge. Your product must have its irreplaceable advantages: fast, effective, cheap with little hurt, etc.

Dr. Chunyu Tan

Q: What are the problems you met in current clinical treatment against tophi and gout?

A: Patients' poor compliance. The disease itself is not hard to treat.

Q: Are there debates on whether patients with hyperuricemia but no obvious symptoms should be recommended to take medications?

A: No. If the uric acid level is less than 600 then patients should have strict control of diet to improve lifestyle and to reduce weight, drugs are not really needed; when the level is more than 600 then drug intervention is required.

Q: Do the current drugs used in gout treatment causing any serious adverse reactions?

A: Medications promoting urate excretion require intact renal function, and drugs inhibiting uric acid synthesis can induce hepatic damage. Some Chinese have a gene making them liable to have allergies such as exfoliative dermatitis after taking allopurinol.

Q: Are patients self-disciplined in diet and taking medications?

A: Really not. It's the biggest problem. 80-90% of patients are not self-disciplined enough.

Q: What do you think of our project?

A: There are few studies on susceptible genes, but there are some clinical phenomena to

consider:

- (1) Patients taking colchicine in the past experienced a decrease in blood uric acid level, and that may be a proof of uric acid excretion in the intestine;
- (2) The number of young patients is increasing, and the reason may not only be lifestyles, but also be problems of metabolic genes in their family; and
- (3) Different patients can develop tophi at very different rates, and that may be because of their different gene types, leading to different subtypes of gout, and the symptoms can be different, too.

Q: What do you think of our treatment in the intestinal tract?

A: Sounds innovating. I do not know much background information about it, but it's a current trend and is worth trying.

Q: What do you think of our treatment with dialysis?

A: I'm not familiar with dialysis, so I cannot provide much advice. But it sounds expensive, and requires knowledge in polymer materials.

Q: Do doctors use dialysis to reduce uric acid to treat some very serious patients?

A: Generally not, unless the patient has renal insufficiency, and meets the indication for dialysis. But to reduce uric acid is not the reason for dialysis; such patients will also be treated with drugs to suppress the synthesis of uric acid.

Dr. Xiaomin Cen

Q: What are the problems you met in current clinical treatment of gout?

A: The patient's compliance is poor. As long as the patients have good compliance, most treatment will be effective. The point is that patients lack perseverance, and only take medications when they feel pain.

But for gout, treatment during remission period is the most important. However, most patients don't understand that, because at the beginning of the disease, it could strike only once or twice a year. After a couple of years or even more than a decade, the organs are harmed, and there are tophi causing chronic arthritis, then patients start to see doctors. The disease can affect the kidneys, so if the patients' kidney functions are no longer intact, and some of them even abuse hormones and anti-inflammatory analgesics, causing gastrointestinal bleeding and ulcer, then these are serious complications can greatly affect our subsequent treatment. Most patients would be well if they had accepted standard treatment once they had any symptoms.

Q: How is patients' compliance?

A: Elderly people have poor compliance. Young people with relatively higher levels of education and a better understanding of the relevant knowledge have good compliance. Education is important.

Q: Are there serious conditions that drug treatment becomes ineffective and the patient cannot

be treated with current methods?

A: Yes, there are. Early patients should be prevented from entering the refractory stage. Patients with refractory gout, such as with broken wounds, are very difficult to recover, so it's hard to help them. Tophi can only be alleviated by a state of long-term low uric acid level.

Q: What do you think of our treatment in the intestinal tract?

A: It has to effectively reduce the blood uric acid level of the model animal, then to have clinical values. Currently our treatment is either to inhibit uric acid synthesis or to promote renal excretion, but for patients with renal insufficiency, the excretion-promoting drugs cannot be used, so it will be good if you can successfully alleviate gout through intestinal excretion. Your idea is innovating and has a good prospect. There are few cases of this kind of patients, so you need do more literature study. Intestinal microbiome is a hot topic. It would be good if you get positive results in animal models.

Q: What do you think of our treatment with dialysis?

A: It's very good. But the uric acid in surrounding tissues doesn't immediately get into the bloodstream. Every dialysis can lower blood uric acid level concentration for a short time, so your device might be reusable. Patients with a risk for oral administration may consider using it.

Q: Are there many patients who are hard to treat?

A: There are some. In the late stage patients have poor renal functions is not good, so tophi are difficult to be excreted, and the number of them keeps increasing. You can't use medicine during a strike, so patients only get hormones. If their digestive tract hemorrhages, hormones can't be used, and the patients can only suffer. No prospects in treatment. The operation cannot clean all tophi and are difficult to heal, and new tophi keep coming. So if you can really lower the uric acid level, and it's fast, then it makes sense. Pay attention to the rate of crystal release, and beware of acute onsets of gout during the release.

Q: Are patients with hyperuricemia but no obvious symptoms recommended to take medications?

A: It depends on the level. If it's 600-700, I recommend medications; if it's just above the level, like 460-470, then diet control will be the first choice. Women before menopause usually do not have gout. And it also depends on the patient's overall situation. If the patient has impaired kidney functions, medications are necessary. If not, start with a diet, and use medications when diet is not very effective. Patients' have very different self-discipline. Those who do not have pain are less disciplined, and those who have repeated pains have a better self-discipline, but the latter usually have genetic problems in metabolizing uric acid and actually require drug control. There are patients who are willing to choose to take medicines to control uric acid level, other than control their diet, for they want a more enjoyable lifestyle.