Review

TCM Researches on Chronic Renal Tubulointerstitial Lesions

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Researches in recent years show that progressive deterioration of the renal function caused by kidney diseases mainly relies on the severity of renal tubulointerstitial lesions (RTIL). Therefore, importance should be attached to RTIL. With its very complicated pathogenesis, RTIL is manifested as the local inflammation in renal interstitium at early stage, followed by secretion of cellular factor and then phenotype variation, apoptosis and excessive proliferation of renal tubular epithelial cell (RTEC), as well as increase in synthesis and decrease in degradation of extracellular matrix (ECM), causing excessive deposition of ECM and eventually renal interstitial fibrosis (RIF). Progress made in TCM researches on RTIL is summarized as follows.

Researches on TCM Syndrome Patterns

In their multi-centered and prospective researches on the law governing the distribution of TCM syndrome patterns and its relationship with nephropathy in 286 cases of IgA nephrosis (IgAN), Chen Xiangmei and others discovered that the syndrome of qi deficiency in the lung and spleen and the syndrome of deficiency of both qi and yin have pathological change mainly at grade I–III of Lee classification, the syndrome of yin deficiency in the liver and kidney mainly at grade III–IV and the syndrome of yang deficiency in the spleen and kidney mainly at grade IV–V. The total score of the syndrome of yang deficiency in the spleen and kidney as well as the scores of renal glomerular and tubular interstitial lesion are much higher than those of other 3 syndrome patterns. The total score of the syndrome of yin deficiency in the liver and kidney and the score of RTIL are much higher than those of other 2 syndrome patterns. The analysis on pathological data of 94 IgAN cases of blood stasis syndrome showed that it is mainly seen at grade III–V of Lee classification with the total score of RTIL and scores of infiltration of interstitial inflammatory cells, interstitial fibrosis and renal tubular atrophy much higher than those of non-blood stasis syndrome. The scores of TCM symptoms and renal biopsy of 409 IgAN cases in another large sample research were divided into 3 kinds respectively. The results indicated: 1) External causes (wind-cold, wind-heat and damp-heat) and internal causes (blood-stasis, phlegm-damp and damp-heat) are obviously related to the infiltration of renal interstitial inflammatory cells and the deposition of tissue immune complex; 2) Internal causes are closely related to cellular proliferation in tissues; and 3) Causes for deficiency of vital qi such as yin deficiency of the liver and kidney and yang deficiency of the spleen and kidney are closely related to RIF and glomerulosclerosis. The above-mentioned 3 researches indicated that IgAN cases of excess syndrome in TCM are mainly manifested as glomerular and tubular interstitial active pathological change while both active and chronic pathological change in blood stasis syndrome accounts for high percentage. The cases of deficiency syndrome in TCM, qi deficiency of the lung and
spleen and deficiency of qi and yin, are mainly manifested as active pathological change while chronic pathological change in yang deficiency of the spleen and kidney and yin deficiency of the liver and kidney accounts for high percentage and severe in degree, especially that of the former. Therefore, it is said that TCM differentiation of symptoms and signs for classification of syndromes is of valuable reference for inferring the pathological change in the kidney of IgAN patients. In their research on TCM syndrome manifestation of 44 patients with chronic aristolochic acid nephrosis (CAAN) mainly manifested as RTIL, Wang Yaoxian and others discovered that the syndrome of deficiency of both qi and yin has the highest incidence of RTIL, and more than 50% of cases of the syndrome of yang deficiency in the spleen and kidney has RTIL when renal function is not yet severely damaged in decompensatory stage, and that the incidence of RTIL in decompensatory stage of blood stasis syndrome is much higher than that of other excess syndromes and rising with the development of disease, indicating that CAAN is characterized by earlier and severe symptoms of yang deficiency and blood stasis on the basis of deficiency of both qi and yin.

**Researches on Chinese Drugs**

1. Single Chinese drug

Huang Qi (黃芪 Radix Astragali Mongolici): On the basis of routine treatment with Western medicine, Chen Liping and others additionally used intravenous drip with 40 ml Huangqi injection to treat 60 cases of primary nephrosis syndrome. They discovered that it is obviously superior in decreasing urine N-acetyl-beta-D-glucosaminidase (NAG), β2-microglobulin (β2-MG), urinary retinol-binding protein (URBP), and 24-hour urine protein to Western medicine group. Its mechanism may be 1) reducing expression of monocyte chemoattractant protein-1 (MCP-1) to decrease aggregation and activation of inflammatory cells in renal tubules and interstitium to alleviate RIF, 2) obviously reducing transforming growth factor-beta (TGF-β1) and βig-h3 (ECM adhesive protein induced by TGF) and expression of mRNA, 3) increasing expression of C-met, the receptor of hepatocyte growth factor of renal interstitial mechanocyte, to play a role in protecting renal tubules and resisting RIF.

Artificial Cordyceps: Wang Yongjun and others used artificial cordyceps to treat 210 RTIL patients with a much better effect than Baoshenkang group in improving creatinine-eliminating rate, urinary osmotic pressure, urine NAG, β2-MG and α1-MG. Its mechanism may be 1) promoting the proliferation of RTEC, reducing cellular lesion or promoting cellular repair and inhibiting the excessive expression of mRNA of RTEC, 2) inhibiting apoptosis of RTEC, and 3) inhibiting the expression of TGF-β and α-smooth muscle actin (α-SMA) and decreasing the transformation of renal tubular epithelial interstitium.

Matrine: It can obviously decrease the expression of connective tissue growth factor (CTGF) and α-SMA of renal tubulointerstitium in unilateral ureteral obstruction (UOO) rat model, partly restore the expression of matrix metalloproteinase 3 (MMP-3), decrease the expression of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), promote the degradation of ECM, and reduce the level of interleukin 6 (IL-6) and the expression of TGF-β1 in adenine rat model, thus play an obvious role in treating experimental RTIL.

Da Huang (大黃 Radix et Rhizoma Rhei Palmati): Researches in recent years confirmed that Da Huang can effectively prevent and treat chronic renal failure (CRF), attributing to rhein and emodin, its main
active ingredients. Emodin can inhibit the proliferation of renal interstitial fibroblasts (RIFS), induce their apoptosis and inhibit cellular growth factors and ECM. Rhein can reverse RTEC overgrowth induced by TGF-β1, inhibit the synthesis of ECM, lower nuclear factor kB (NF-kB) and activity of Caspase-3, reduce apoptosis of RTEC.\textsuperscript{16} Obstruct multiplication of RIFS induced by TGF-β1, inhibit RIFS activated by TGF-β1 and antagonize expression and synthesis of fibronectin (FN).\textsuperscript{17} According to the pharmacokinetic experiment on human body, Zhu Wei pointed out recently that rhein may be the sole active ingredient of Da Huang (大黄 Radix et Rhizoma Rhei Palmati) to treat CRF.\textsuperscript{18}

Panax notoginseng saponins (PNS): PNS can inhibit excessive multiplication of RTEC induced by uremic serum and secretion of total collagen to raise MMP-1/TIMP-1 (ratio of genetic expression to protein secretion) which plays an important role in the occurrence of RIF, promote degradation of ECM,\textsuperscript{19} increase the expression of proliferating cell nuclear antigen (PCNA) in RTEC, decrease the expression of α-SMA, reduce the expression of PCNA and α-SMA in RIFS, inhibit transdifferentiation of RTEC induced by TGF-β1 and IL-1α,\textsuperscript{20,21} thus giving play to the effect of preventing and treating RTIL.

Glycyrrhizic acid (GA): Wang Huiling and others\textsuperscript{22} found that GA can remarkably improve the excretion of urine albumin and NAG and the level of blood creatinine in CAAN animal model group with an effect similar to that of prednisone. Its mechanism may be 1) inhibiting the generation and expression of Ang II and osteopontin in renal tissue and reducing the expression of TGF-β1 and CTGF to decrease transdifferentiation of RTEC and synthesis of ECM,\textsuperscript{26,27} 2) lowering the expression of tissue transglutaminase (tTG) which can make ECM protein chain form stable structure to resist the degradation of ECM,\textsuperscript{28} 3) continuously strengthening the activity of endothelial nitric oxide synthase (ENOS) in renal tissue of UUO rat model to increase nitric oxide (NO) to reduce angiotasis and relieve ischemia and hypoxia in the kidney,\textsuperscript{29} and 4) inhibiting the expression of bax, an antiapoptotic component in RTEC, and lowering the Bcl-2/bax to inhibit apoptosis of RTEC.\textsuperscript{30}

Hong Hua (红花 Flos Carthami): Ding Yueling and others found that Hong Hua can remarkably protect impaired RTEC to reduce RIF. Its mechanism is closely related to inhibiting TGF-β1 and genetic expression of mRNA and c-fos.\textsuperscript{25}

In addition, Dan Shen (丹参 Radix Salviae Miltiorrhizae), Ligustrazine, Hong Jing Tian (红景天 Radix Rhodiola), Triptolide, and Ginsenoside also have obvious effect of preventing and treating RTIL.

2. Compound of Chinese drugs

Formulation made from Huang Qi (黄芪 Radix Astragali Mongolici) and Dang Gui (当归 Radix Angelicae Sinensis). Scholars found in recent years that this recipe is good for preventing and treating RTIL with the effect similar to the angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB). Its mechanism may be 1) inhibiting the generation and expression of Ang II and osteopontin in renal tissue and reducing the expression of TGF-β1 and CTGF to decrease transdifferentiation of RTEC and synthesis of ECM,\textsuperscript{26,27} 2) lowering the expression of tissue transglutaminase (tTG) which can make ECM protein chain form stable structure to resist the degradation of ECM,\textsuperscript{28} 3) continuously strengthening the activity of endothelial nitric oxide synthase (ENOS) in renal tissue of UUO rat model to increase nitric oxide (NO) to reduce angiotasis and relieve ischemia and hypoxia in the kidney,\textsuperscript{29} and 4) inhibiting the expression of bax, an antiapoptotic component in RTEC, and lowering the Bcl-2/bax to inhibit apoptosis of RTEC.\textsuperscript{30}

Shenyan Fangshuai Ye (肾炎防衰液 Renal failure-preventing liquid). It consists of Huang Qi (黄芪 Radix Astragali Mongolici), Dang Gui (当归 Radix Angelicae Sinensis), Hong Jing Tian (红景天
Radix Rhodiola), Zhi Da Huang (制大黃 Radix et Rhizoma Rhei Preparata), E Zhu (莪术 Rhizoma Curcumae) and Liu Yue Xue (六月雪 Herba Serissae). Its effect of reducing 24 h urine protein, NAG, serum creatinine (SCr) and blood urea nitrogen (BUN) in rats with obstructive renal failure is similar to that of Benazepril. Its mechanism may be lowering the expression of TGF-β1 to decrease the level of α-SMA, alleviate the excessive expression of collagen and delay the progress of RIF.

Yishen Ruanjian San (益腎軟堅散 Nourishing kidney and resolving mass powder). It consists of eight Chinese drugs including Huang Qi (黄芪 Radix Astragali Mongolici), Dang Gui (當歸 Radix Angelicae Sinensis), Dan Shen (丹蔘 Radix Salviae Miltiorrhizae), Zhi Bie Jia (鳖甲 Carapax Trionycis Preparata) and Cordycepic mycelia. Chen Yipu and others confirmed in their research in vitro that this serum-containing recipe can reduce the expression of TGF-β1, CTGF and TIMP-1 and mRNA of human RIFS and RTEC to antagonize AA-caused ECM accumulation but have no obvious influence on plasminogen activator inhibitor-1 (PAI-1). They also confirmed that this recipe can reduce the expression of the above-mentioned indexes including PAI-1 in renal tissues to relieve RIF of CAAN.

Shenluo Tong (腎絡通 Clearing renal collaterals drug). It consists of Huang Qi (黄芪 Radix Astragali Mongolici), Dang Gui (當歸 Radix Angelicae Sinensis), Dan Shen (丹蔘 Radix Salviae Miltiorrhizae), Chuan Xiong (川芎 Rhizoma Chuanxiong), Di Long (地龍 Pheretima Aspergillum), Wu Shao She (烏梢蛇 Zaocys), Da Huang (大黃 Radix et Rhizoma Rhei) and Jiang Can (僵蚕 Bombyx Batryticatus). Ding Yueling and others discovered that the recipe can alleviate pathological change in ultrastructure of renal tubules to protect RTEC. Its mechanism may be inhibiting the expression of renal tubular interstitial PCNA, and decreasing the expression of α-SMA, fibronectin (FN) and laminin (LN) through reducing renin activity and Ang II level and lowering the expression of TGF-β1 and mRNA to delay RIF.

Fufang Biejia Ruangan Pian (复方鳖甲软肝片 Compound tortoise shell tablet for softening liver). It consists of Huang Qi (黄芪 Radix Astragali Mongolici), Dang Gui (当归 Radix Angelicae Sinensis), Bie Jia (鳖甲 Carapax Trionycis), San Qi (三七 Radix Notoginseng), Chi Shao (赤芍 Radix Paeoniae Rubra), Dong Chong Xia Cao (冬虫夏草 Cordyceps) and Lian Qiao (连翘 Fructus Forsythiae). This is a new drug with definite effect of resisting hepatic fibrosis. Zhao Zongjiang and others proved in a series of researches that the recipe can obviously inhibit the expression of NF-κB and TGF-β1 and mRNA in renal tissue of UUO rats with an effect similar to that of Benazepril. It can also remarkably increase the expression of MMP-9 in UUO rats, decrease the expression of TIMP-1 and promote the degradation of ECM to prevent and treat RIF effectively.

Conclusion

The above-mentioned researches show that TCM syndrome patterns are instructive for inferring the pathological change in RTIL. The Chinese drugs mentioned above supplement qi, nourish the kidney, promote blood circulation, remove blood stasis, clear heat and eliminate toxin. From the response of the disease to the drugs applied, it can be suggested that deficiency of the spleen and kidney, blood stasis and toxic heat may be the main pathogenesis of RTIL. However, because of its complication and variation, there have been no enough systematic and profound researches on Chinese drugs for clinical treatment. As molecular biology is further adopted in TCM, the relationship between Chinese drugs and RTIL will be inevitably determined. Application of Chinese drugs
based on differentiation of syndromes guided by TCM theory will be prosperous in future.

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(Translated by DUAN Shu-min 段树民)