Herbs and Immunosuppressive Drugs

Calcineurin Inhibitors

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Abstract

The calcineurin-inhibiting drugs cyclosporine and tacrolimus are very commonly used in patients after organ transplantation, as well as in some patients with severe autoimmune diseases. However, these drugs can cause severe adverse effects, including kidney damage (particularly problematic in people who have undergone kidney transplantation), diabetes, dyslipidemia, hypertension, and many other problems.

Some herbal medicines, particularly *Cordyceps sinensis* = *Ophiocordyceps sinensis* (cordyceps) mycelium, have been shown to enhance the efficacy—while decreasing the toxicity—of cyclosporine. Other herbs that may be helpful for patients who are taking cyclosporine include *Glycyrrhiza uralensis* (Chinese licorice), *Astragalus membranaceus* (astragalus), and *Allium sativum* (garlic). Fish oil may also be beneficial for people who are taking cyclosporine. Dose-sparing agents for potential use with cyclosporine include *Citrus* x *paradise* (grapefruit) and *Geum chiloense* = *G. quellyon* (scarlet avens).

Hypericum perforatum (St. John's wort) can interfere with cyclosporine and tacrolimus and should not be taken simultaneously with these drugs. Herbs that can be beneficial in combination with tacrolimus include *Camellia sinensis* (green tea), *Isatis tinctoria* (woad), *Schisandra sphenanthera* (southern schisandra), grapefruit, and *Citrus grandis* (pomelo)—provided the tacrolimus dose is reduced—as well as *Paeonia lactiflora* (white peony) and *Tripterygium wilfordii* (thunder duke vine*). The details of these and other interactions are reviewed in this article

*Although this herb is frequently called "thunder god vine," this is a mistranslation, which was confirmed by Dan Bensky, DO (an expert translator and author of one of the most widely used and revered English-language Chinese herbal materia medicas), in a personal communication. While almost all Western literature uses this common name, the current authors believe that it is important to start using a more-correct translation rather than perpetuating what is clearly an error that is being unknowingly propagated.

Introduction

Immunosuppressive drugs of various types (Table 1) have made organ transplantation possible and are widely used for this purpose. These drugs also help many patients who have autoimmune diseases. The drugs can be lifesaving in patients with severe, acute autoimmune diseases and can delay progression of chronic disease. However, the drugs do not cure patients and have to be taken continuously, chronically suppressing symptoms. This exposes patients to the long-term toxicities of the drugs—toxicities that can be substantial. In some cases, these side-effects are more troubling than the long-term effects of untreated disease. This article does not deal with newer biologic immunosuppressive drugs, such as tumor necrosis factor-α inhibitors, as there is not, as yet, research on the possibility of herbs to be combined with these newer agents safely and effectively.

All immunosuppressive drugs, of course, potentially expose patients to increased risk of cancers and infections. This is an inevitable result of immunosuppression, although this, fortunately, only affects a minority of patients. All immunosuppressive drugs have a host of other drug-specific toxicities that can be quite significant (Table 1).

This article reviews the role herbal medicines have to play both in enhancing the efficacy of calcineurin-inhibiting immunosuppressive drugs and decreasing or abrogating their toxicity. Mainstream clinicians have been told repeatedly that patients who are taking cyclosporine or tacrolimus should be advised to avoid using herbs or foods that interfere with cytochrome CYP 3A4 or P-glycoprotein (Pgp) enzymes, because of the narrow therapeutic windows of these drugs. Clinicians have also been told that patients should avoid using immunomodulating† herbs that could reverse the effects of the drugs.

†Note that herbs that are considered immunostimulating or that have not specifically been studied in combination with immunosuppressive drugs should be withheld from patients until further information is available.

DOI: 10.1089/act.2013.19605 • MARY ANN LIEBERT, INC. • VOL. 19 NO. 6 DECEMBER 2013

Table 1. Overview of Major Immunosuppressive Drugs

Drug	Mechanism(s)	Toxicities
Cyclosporine	Calcineurin inhibitor (reduces IL-2)	Nephrotoxic (renal fibrosis), gingival hyperplasia, hypertension, diabetes, neurotoxicity
Tacrolimus	Calcineurin inhibitor (reduces IL-2)	Nephrotoxic, hypertension, diabetes, neurotoxicity
Sirolimus	Inhibits mTOR1 (blocks activity of IL-2)	Interstitial pneumonitis, diabetes, impaired wound healing, thrombocytopenia
Glucocorticoids	Inhibit IL-2, other cytokines; inhibit PLP	Cushing's syndrome, growth retardation, impaired wound healing, increased IOP, osteoporosis, hyperglycemia
Azathioprine	Purine analogue	Myelotoxicity, hepatotoxicity, mutagenic
6-mercaptopurine	Purine analogue	Myelotoxicity, hepatotoxicity, mutagenic, diabetes, acute pancreatitis
Mycophenolate	Guanosine synthesis inhibitor	Diarrhea
Methotrexate (low-dose)	Dihydrofolate reductase inhibitor	GI upset
Cyclophosphamide	DNA alkylator	Myelosuppression, alopecia, malaise, hemorrhagic cystitis, acute myeloid leukemia, bladder cancer, sterility

IL, interleukin; IOP, intraocular pressure, PLP, phospholipase; GI, gastrointestinal.

This article provides numerous examples from the published medical literature that challenge these proscriptions, and, in some cases, show how the converse may be true—that a more-effective treatment approach is to combine the herb and the drug. Caution is warranted when making any such combination, given the relatively high stakes involved, particularly after an organ transplant. This article points out where problems exist and when combination should be avoided. However, the major burden of toxicity of these drugs can be significantly offset for many patients by using herbal therapies, and fear should not restrain such combination therapy unduly. In a subsequent article, other categories of immunosuppressive drugs will be considered.

Cyclosporine and Immunomodulators

Cyclosporine (var. ciclosporin, cyclosporin) is a commonly used, 11–amino-acid, polypeptide immunosuppressant used in patients who have had kidney (among other types of) transplants, but the agent has the significant problem of being nephrotoxic.[1] The problem is that the drug actually damages arteries that then cause renal fibrosis, as well as damaging the liver and other organs (including other transplanted organs).

Chronic cyclosporine therapy also increases insulin resistance, thus degrading glucose tolerance; induces hypertriglyceridemia and elevates low-density lipoprotein cholesterol levels; increases the risk of developing many types of cancer; induces gingival hyperplasia; and increases risk of infections, particularly cytomegalovirus.[2] The original formulation of cyclosporine, in which it was mixed with oil (Sandimmune™ by Novartis), led to significantly more adverse effects than the newer microemulsion form of the drug (Neoral™ by Novartis). But even the microemulsion form leads to substantial rates of severe adverse effects with long-term use. No other immunosuppressive drug has undergone as extensive research in combination with herbs as has cyclosporine.

The immunomodulatory, endoparasitic[‡] fungus *Ophiocordyceps sinensis*, formerly known as *Cordyceps sinensis*, is called cordyceps in English, *dōng chóng xià cǎo* ("winter worm, summer grass") in Mandarin Chinese, and *yartsa gunbu* (same translation as Mandarin Chinese) in Tibetan. The related species *Cordyceps militaris* is also used as a medicine. *O. sinensis* is native to the Tibetan plateau. There is some evidence from other human studies that cordyceps blocks transforming growth factor-beta-1 (TGF-β1), a cytokine enhanced by cyclosporine associated with chronic allograft nephropathy (CAN).[3]

Unfortunately, the fruiting bodies of this fungus have been severely overharvested because of poor local economic opportunities for indigenous Tibetans, and thus, it is inadvisable to purchase wild cordyceps, lest it be made extinct in the wild.[4] Vat-grown mycelium is a good alternative. As a side note, cyclosporine was originally isolated from *Cordyceps subsessilis* (formerly *Tolypocladium inflatum*), and at least traces of this compound are found in *O. sinensis*.[5]

In a clinical trial of 202 Chinese patients who underwent kidney transplantation and received cyclosporine, mycophenolate, and prednisone, half of the patients were randomly assigned to also receive cordyceps dry mycelium powder (1 g t.i.d.).[6] There was a significant reduction in CAN and hepatotoxicity in the cordyceps group, compared to the control group, after 1 year, with no difference in graft or overall survival or acute graft rejection between the groups at that time. Urine total protein levels and cyclosporine doses were significantly lower in the cordyceps group, compared to the control group. There was no difference in trough cyclosporine blood levels,

[‡]This means that the fungus infects arthropods, insects, and other fungi, resulting in formation of a fruiting body that replaces the other organism's body.

suggesting that the cordyceps was helping immune control rather than just reducing adverse effects or acting via a pharmacokinetic interaction.

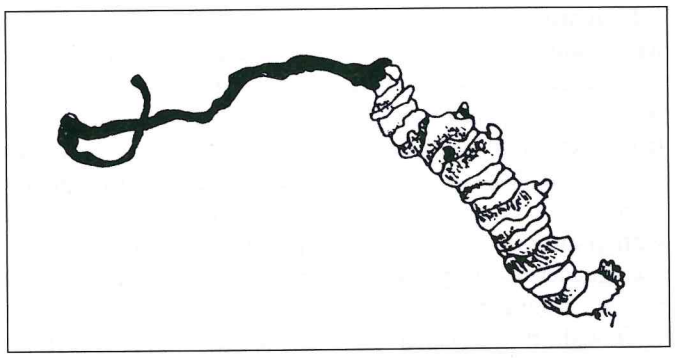
In a trial of 84 Chinese patients with CAN associated with cyclosporine, 22 were randomly assigned to take cordyceps mycelium powder (2 g b.i.d.) with an angiotensin-converting enzyme–inhibiting drug (10 mg of enalapril q.d.), 21 to take cordyceps alone, 20 to take enalapril alone, and 21 to an additional treatment.[7] After 6 and after 9 months, the combination therapy group had a greater reduction in urine-protein excretion, better graft stabilization, and reduced CAN progression, compared to either of the treatments on their own, and compared to the control condition. Enalapril and cordyceps on their own were significantly superior to the control conditions with respect to measures.

A group of 231 Chinese patients with cyclosporine-related CAN were randomly assigned to add either cordyceps dry mycelium powder (2 g t.i.d.) or no additional therapy for 6 months.[8] Serum creatinine and creatinine clearance improved in the cordyceps group, compared to baseline; no such improvement was seen in the control group. Significantly more patients in the cordyceps group had renal functional improvement, compared to the control group (72/122 for the cordyceps group versus 14/109 for the control group). This trial confirms the results of an earlier, nonrandomized, 3-month trial comparing 36 patients who had CAN and were taking cordyceps powder (3 g t.i.d.) to 15 patients who had CAN but no additional therapy.[9]

In a rodent model of heart transplantation, a combination of an oral aqueous extract of cordyceps (3.4 mg/mL dose) with a subtherapeutic dose of cyclosporine prevented acute rejection, decreased CD8+ T-lymphocyte activity, and prevented allograft vasculopathy.[10] Cordyceps by itself did not prevent any acute rejection (not surprising given that this herb's main influences seem to be on CD8+ and not CD4+ T-cells), and subtherapeutic cyclosporine was also quite ineffective for preventing rejection. The low molecular weight fraction of the cordyceps extract was the most active fraction in this model.

Glycyrrhiza uralensis (Chinese licorice, *gān cǎo* in Mandarin Chinese) root is another immunomodulator with nephroprotective effects. Although there is much less study of it in combination with cyclosporine, one case series found that Chinese licorice was effective for treating acute hemorrhagic cystitis and nephropathy caused by an adenovirus.[11] Glycyrol, a benzofuran found in Chinese licorice root, has been shown to inhibit calcineurin itself, along with having many other inflammation-modulating actions.[12,13] However, as will be shown below, there may be a pharmacokinetic reason to avoid combining licorice with cyclosporine.

As yet, other immunomodulating herbs do not appear to have been studied in combination with cyclosporine but the above studies set the stage for the potential for benefits of such combinations. One such plant is *Astragalus membranaceus* (astragalus, *huáng qí*) root, which downregulated CD4+ T-cell activity and upregulated T-reg activity in rodents having undergone skin transplantation when given by intravenous injections.[14] The effects of the astragalus injection and cyclosporine were very similar in this study. Further research is absolutely warranted.



Ophiocordyceps sinensis (cordyceps). Drawing ©2013 by Eric Yarnell, ND, RH (AHG).

Pharmacokinetic Interactions with Cyclosporine

Cyclosporine is a substrate for CYP3A4 and Pgp, particularly in the small intestinal epithelium. Cyclosporine also inhibits CYP3A4 and Pgp. Thus, cyclosporine can have interactions with substances that affect either of these and can interact with substances that are other substrates for CYP3A4 and/or Pgp.

When Chinese licorice, or its potent triterpenoid saponin, glycoside glycyrrhizin, was given to rats simultaneously with cyclosporine, peak blood concentrations and total exposures to the drug were reduced.[15] This decrease was attributed to induction of CYP3A4 and Pgp primarily through the effects of glycyrrhetinic acid, the principal metabolite of glycyrrhizin.

In vitro, glycyrrhetinic acid has been shown either to inhibit human CYP3A4 or to have no effect on it.[16,17] Other studies in rats have found that glycyrrhizin can inhibit CYP3A4.[18] The one human case series involving Chinese licorice and cyclosporine[11] reported no pharmacokinetic interactions, although both substances were only combined for a short period of time. Therefore it is highly unclear whether or not licorice would interact pharmacokinetically with cyclosporine, but serum levels of the drug should be followed (as they almost always are) to ensure that this does not happen with any particular patient.

Various citrus fruits, notably the juice from grapefruit (*Citrus* x *paradise*), contain furanocoumarins, such as bergamottin, that inhibit intestinal CYP3A4 and Pgp.[19] Because of this, grapefruit juice can serve as a dose-sparing agent for cyclosporine, particularly the older, poorly absorbed oil-based formulation, as the juice decreases degradation of the drug before it enters the body. Starting in the mid-1990s, trials in patients with transplants documented that grapefruit juice could increase systemic exposure to cyclosporine by an average of 32% with wide interindividual differences.[20,21]

Intravenous cyclosporine is not affected by oral grapefruit juice, which suggests strongly that the interaction occurs in the intestinal wall and not in the liver or elsewhere in the body.[22] Later research showed that absorption of microemulsion cyclosporine is also significantly increased by grapefruit juice.[23]

In another study, patients with autoimmune diseases who were taking cyclosporine also had an increase in absorption on average when combining it with grapefruit juice, to the point that 1 patient developed neurologic adverse effects from excessive cyclosporine levels.[24] Another study has shown that African Americans have a significantly greater increase in cyclosporine exposure when the drug is combined with grapefruit juice than white people do (60% versus 44% average increase, respectively, in area under the curve between the two groups).[25]

Though this research generally suggests that grapefruit juice could be used to decrease the dose of cyclosporine without affecting efficacy, the variation between batches of juice and interindividual variability in response to grapefruit have made this clinically very challenging.[26] Therefore, until—and unless—a standardized product is put on the market, or unless there is very careful monitoring of trough cyclosporine levels (particularly when switching brands or batches of products), grapefruit juice, pomelo (*Citrus grandis*), and other bitter citrus fruits (whole or in juices) should probably not be combined with cyclosporine.[27]

Geum chiloense, also called *G. quellyon* (scarlet avens, *hierba de clavo*), was reported to cause massive elevation of serum levels of cyclosporine in a 54-year-old man with a renal transplant.[28] When this patient stopped taking the herb, his cyclosporine levels normalized with no change in cyclosporine dose. This suggests the potential for this herb to be used as a dose-sparing agent with cyclosporine, pending further study.

Hypericum perforatum (St. John's wort) leaf and flower contain hyperforin, a prenylated phloroglucinol, that is well-established as a pregnane X receptor (PXR) agonist.[29] This leads to induction of CYP3A4 and many drug interactions in some patients; recent genetic research suggests that differences in PXR alleles among people might explain the variability of responses to St. John's wort.[30] Several case reports initially suggested that St. John's wort might interfere with cyclosporine absorption.[31] In a study of 11 patients who received renal transplants, 600 mg of a St. John's wort extract daily for 2 weeks dramatically reduced these patients' cyclosporine levels.[32] Hyperforin was clearly to blame for this specific drug interaction.[33] St. John's wort extracts containing hyperforin should *not* be used in patients who are taking cyclosporine.

Some other herbs may have an influence on the pharmacokinetics of cyclosporine. Purple grape juice and red wine can both also decrease absorption of cyclosporine substantially (by 30% on average) in humans, and thus, combination of these beverages with cyclosporine should be avoided.[34,35]

Scutellaria baicalensis (Chinese skullcap, *huáng qín*) root decoction decreased absorption of cyclosporine in rats, while isolated flavonoids of the herb had the opposite effect.[36] This study was interesting because it supported a common conjecture in herbal medicine (made by many herbalists including the current authors) that whole-herb extracts are different than their isolated constituents.

Zingiber officinale (ginger) rhizome juice also decreased absorption of cyclosporine in rats.[37] This is strange, because ginger commonly increases absorption of most substances, and there is no way to be sure what it would do in humans, but caution is warranted.

Miscellaneous Interactions with Cyclosporine

Cyclosporine frequently causes dyslipidemia and oxidation of low-density lipoprotein cholesterol. *Allium sativum* (garlic) was assessed in a trial involving 50 Iranian patients who received renal transplants.[38] All were taking cyclosporine, prednisone, and azathioprine (or mycophenolate). These patients each added 1

Fish Oil and Cyclosporine

Although fish oil is not an herbal remedy, it would be remiss to not mention this supplement. It has been extensively studied as an adjunct therapy with cyclosporine. Several randomized, double-blinded, controlled trials have shown that 3-4 g of fish oil per day in patients who have had cardiac transplants helps maintain normal blood pressure (BP) or reduce BP.[a–c]

At least one trial found a similar benefit in patients who have received renal transplants.[d] One study, using the relatively large dose of 12 g of fish oil per day in patients who received liver transplants reported a substantial nephroprotective effect in just 2 months.[e] There are conflicting results regarding whether or not fish oil prevents acute rejection or prevents nephrotoxicity.[f,g] One trial found that a combination of 1 g of fish oil and 20 mg of pravastatin was more effective than pravastatin alone for correcting cyclosporine-induced dyslipidemia in patients who had received kidney transplants and who were not helped by dietary changes alone.[h]

These studies have all been relatively small, so they were either underpowered to detect significant results or, by chance, had inaccurately positive results.[i] Larger clinical trials are warranted to resolve finally what role fish oil has in combination with cyclosporine.

[a]Ventura HO, Milani RV, Lavie CJ, et al. Cyclosporine-induced hypertension: Efficacy of omega-3 fatty acids in patients after cardiac transplantation. Circulation 1993;88:II281–II285; [b]Andreassen AK, Hartmann A, Offstad J, et al. Hypertension prophylaxis with omega-3 fatty acids in heart transplant recipients. J Am Coll Cardiol 1997;29:1324–1331; [c]Holm T, Andreassen AK, Aukrust P, et al. Omega-3 fatty acids improve blood pressure control and preserve renal function in hypertensive heart transplant recipients. Eur Heart J 2001;22:428–436; [d]Santos J, Queirós J, Silva F, et al. Effects of fish oil in cyclosporine-treated renal transplant recipients. Transplant Proc 2000;32:2605–2608; [e]Badalamenti S, Salerno F, Lorenzano E, et al. Renal effects of dietary supplementation with fish oil in cyclosporine-treated liver transplant recipients. Hepatology 1995;22:1695–1671; [f]van der Heide JJ, Bilo HJ, Donker JM, et al. Effect of dietary fish oil on renal function and rejection in cyclosporine-treated recipients of renal transplants. N Engl J Med 1993;329:769–773; [g]Kooijmans-Coutinho MF, Rischen-Vos J, Hermans J, et al. Dietary fish oil in renal transplant recipients treated with cyclosporin-A: No beneficial effects shown. J Am Soc Nephrol 1996;7:513–518; [h]Busnach G, Stragliotto E, Minetti E, et al. Effect of n-3 polyunsaturated fatty acids on cyclosporine pharmacokinetics in kidney graft recipients: A randomized placebo-controlled study. J Nephrol 1998;11:87–93; [i]Lim AK, Manley KJ, Roberts MA, Fraenkel MB. Fish oil for kidney transplant recipients. Cochrane Database Syst Rev 2007;2:CD005282.

clove of garlic per day to their regimens and were randomized to either chew or swallow the clove whole. In patients who chewed the cloves, total cholesterol, triglycerides, diastolic blood pressure (BP), and malondialdehyde (MDA; a marker of oxidation) levels were significantly decreased, compared to patients who swallowed the cloves whole. Compared to baseline, swallowing garlic decreased systolic BP and MDA levels significantly, and chewing garlic decreased systolic and diastolic BP, triglycerides, total cholesterol, and serum creatinine significantly. Garlic had no effect on serum levels of cyclosporine.

This human study confirms earlier reports of a hypolipidemic effect of garlic in rats treated with cyclosporine.[39] Rodent studies found that *Camellia sinensis* (green tea) helped prevent cyclosporine-induced nephrotoxicity by inducing regrowth of mitochondria and by inhibiting TGF-β1.[40,41] Other miscellaneous preclinical interactions reported between herbs and cyclosporine are summarized in Table 2.

Tacrolimus

Tacrolimus is a calcineurin-inhibitor originally derived from the bacterium *Streptomyces tsukubaensis*. It is also frequently referred to as FK506 in the literature and sometimes as fujimycin. It acts very similarly to cyclosporine, and the two drugs' adverse-effects profiles are similar. Structurally, tacrolimus is similar to macrolide antibiotics, such as erythromycin. In addition, like cyclosporine, tacrolimus is also metabolized by/acted on by CYP3A4 and Pgp.

Like cyclosporine, it appears that tacrolimus, in part, causes nephrotoxicity by inducing free radicals that damage blood vessels and tubular cells; other toxic effects of these drugs may also relate to the oxidative damage they cause.[42] Green tea flavonoids were shown to help prevent this in rodents given tacrolimus or cyclosporine, in large part because of the flavonoids' antioxidant nature.[43,44] Human clinical trials have found that vitamins E and C taken with tacrolimus and cyclosporine can decrease the oxidative damage they cause.[45]

Isatis tinctoria (woad, *bǎn lán gēn*) root is an antimicrobial and immunomodulating herb historically used in Asia and Europe. An unsaturated fatty acid from the leaf was found to be strongly immunosuppressive, and analogues of it have been developed that allowed use of subtherapeutic doses of tacrolimus to suppress heart-transplant rejection in rodents.[46] The efficacy of the combination was better than full-dose tacrolimus by itself, and the combination was safer. Inhibition of interleukin-2 appeared to be the main mechanism involved.

Schisandra chinensis (northern schisandra, *běi wǔ wèi zǐ*) and *S. sphenanthera* (southern schisandra, *nán wǔ wèi zi*) are two largely interchangeable vines that originate in China, although northern schisandra is more frequently encountered in the United States. The fruits of these herbs are used as medicines and contain compounds with all major tastes (the Mandarin Chinese name literally translates to "five flavor fruit"). These are immunomodulating and hepato- and nephroprotective herbs.[47]

Southern schisandra, in particular, has been shown repeatedly to increase absorption and systemic exposure to tacrolimus.[48] CYP3A4 or Pgp inhibition in the gut are the likely reasons for this interaction.[49] Schisandra's lignans, including schisandrin A and B and gomisin A, are believed to be critical for the effects of northern and southern schisandra on tacrolimus.

Table 2. Cyclosporine and Miscellaneous Natural Adjuncts in Preclinical Studies

Herb (common name)	Interaction	Authors, year
Allium ascalonicum (shallot)	Decreases nephrotoxicity of cyclosporine in rats	Wongmekiat et al., 2008[a]
Allium sativum (garlic)	Reduces oxidative damage in the kidneys of rats treated with cyclosporine	Durak et al., 2007[b]
Geum japonicum = *G. macrophyllum* (large leaf avens)	Suppressed cytomegalovirus in mice immunosuppressed by cyclosporine	Yukawa et al., 1996[c]
Heteropterys aphrodisiaca (*nó-de-cachorro*)	Largely prevents testicular damage by cyclosporine in rats	Monteiro et al., 2008[d]
Salvia miltiorrhiza (red sage)	Decreased TGF-β and renin levels in kidneys of rats treated with cyclosporine	Qiao et al., 2001[e]
Syzygium aromaticum (clove)	Suppressed cytomegalovirus in mice immunosuppressed by cyclosporine	Yukawa et al., 1996[c]
Terminalia chebula (chebulic myrobalan)	Suppressed cytomegalovirus in mice immunosuppressed by cyclosporine	Yukawa et al., 1996[c]
Vitis vinifera (black grape)	Reduced oxidative damage in the kidneys of rats treated with cyclosporine	Durak et al., 2007[b]

[a]Wongmekiat O, Leelarugrayub N, Thamprasert K. Beneficial effect of shallot (*Allium ascalonicum* L) extract on cyclosporine nephrotoxicity in rats. Food Chem Toxicol 2008;46:1844–1850; [b]Durak I, Cetin R, Candir O, et al. Black grape and garlic extracts protect against cyclosporine A nephrotoxicity. Immunol Invest 2007;36:105–114; [c]Yukawa TA, Kurokawa M, Sato H, et al. Prophylactic treatment of cytomegalovirus infection with traditional herbs. Antivir Res 1996;32:63–70; [d]Monteiro JC, Predes FS, Matta SL, Dolder H. *Heteropterys aphrodisiaca* infusion reduces the collateral effects of cyclosporine A on the testis. Anat Rec (Hoboken) 2008;291:809–817; [e]Qiao BP, Tang XD, Ruan Q. Experimental study of compound salvia injection in preventing and treating chronic nephrotoxicity induced by cyclosporin A in rats [in Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2001;21:611–614.

Deliberate attempts to combine schisandra extracts with tacrolimus have been undertaken to reduce the necessary doses, and thus costs and toxicity, of tacrolimus. In one study, 64 patients who received renal transplants, and who were taking tacrolimus, prednisone, and mycophenolate, were randomly assigned to take southern schisandra extract (dose not stated beyond "one capsule twice daily") or no additional therapy for 6 months.[50] Blood concentrations of tacrolimus rose significantly despite doses being decreased in the schisandra group, while such changes were not nearly as dramatic in the control group. Serum aminotransferase levels fell significantly in the schisandra group, compared to baseline but did not change in the control group. Given that the average dose reduction was almost 40% in the schisandra group, and that the tacrolimus they were using (in China) cost $4.33/mg, and that the schisandra capsules cost $0.15 each, the researchers calculated that each patient saved $2,135 per year in costs with this combination.

Forty-six patients in China who received liver transplants were given either usual dose of tacrolimus alone or southern schisandra extract (dose unknown) and a lowered dose of tacrolimus.[51] The combination group had higher levels of tacrolimus in their blood than the patients who were taking tacrolimus alone; yet the combination group's serum transaminases were decreased, compared to baseline, while these in patients in the tacrolimus-only group were not. Furthermore, less diarrhea and agitation were seen in the combination group. This also seems to suggest that schisandra can be used as a dose-sparing adjunct to tacrolimus that simultaneously lowers the drug's toxicity.

Bitter citrus, including pomelo and grapefruit, as CYP3A4 and Pgp inhibitors, can also be used as dose-sparing agents for tacrolimus.[52] In one published human case study, a 28-year-old Japanese woman who received a new liver developed rejection 4 years after transplantation.[53] Her blood levels of tacrolimus could not be kept in the therapeutic range and, so, finally she took 250 mL of grapefruit juice with her usual tacrolimus dose. This led to dramatic increases in tacrolimus absorption but also headaches and nausea. No other toxicities could be detected during this period. The patient could not tolerate the taste of the juice and discontinued it after 4 days.

While the researchers concluded that grapefruit should not be combined with tacrolimus as a result of what they observed in this case, it should be noted that the researchers made no effort to adjust this patient's tacrolimus dose, to see if there was a tolerable combination.[53] Apparently, they also made no effort to have the patient simply mix the grapefruit juice with other juices to make it tolerable.

In one rat study, *Curcuma longa* (turmeric) rhizome and ginger juices also increased absorption of tacrolimus.[54] This was the opposite effect seen with ginger juice and cyclosporine noted above, which is surprising and makes it clear that we have no idea what ginger or turmeric would do to tacrolimus levels in humans.

Paeonia lactiflora (white peony, *bái sháo*) is a common Chinese herbal medicine containing glycosides that have been studied for their ability to enhance the efficacy of tacrolimus. In a rat model of heart transplantation, a total glycoside extract of white peony root was combined with tacrolimus and compared to control rats treated only with tacrolimus.[55] Graft survival was significantly longer in the white peony + tacrolimus group, compared to the control group. Levels of T-helper lymphocytes were significantly lower in the combination group, compared to the control group; T-killer lymphocyte levels were not different. There was no difference in the toxicity of tacrolimus between the groups. This suggests that white peony has a beneficial pharmacodynamic interaction with tacrolimus, without affecting pharmacokinetics.

Tripterygium wilfordii (thunder duke vine,* *léi gōng téng*) is a vine native to China, in the Celastraceae family, that contains immunosuppressive glycosides, particularly triptolide.[56] The decorticated bark extracts of thunder duke vine are safest but still carry significant risks including anemia, menstrual irregularities, and male and female infertility.

In a trial involving 22 Chinese patients who received kidney transplants and who had signs of calcineurin inhibitor–induced nephrotoxicity, an unspecified extract and dose of thunder duke vine was added to their tacrolimus-containing immunosuppression regimens.[57] Trough levels of serum tacrolimus increased significantly with addition of thunder duke vine. Eight of 12 patients with proteinuria and 5 of 6 patients with hematuria had their problems alleviated by adding thunder duke vine, and 3 of 4 patients with rising serum creatinine levels had them stabilize or decrease.

However, 2 patients developed new-onset liver dysfunction that was reversed with discontinuation of thunder duke vine.[57] One patient developed diarrhea, 3 developed infections, and 2 developed leukopenia, but all of these adverse effects are common with the immunosuppressive drugs these patients were already taking, so it is difficult to attribute these effects to thunder duke vine. A pharmacokinetic interaction could not be ruled out but CYP3A5 genotype did not influence the interaction.

St. John's wort interferes with absorption of oral tacrolimus. Studies in healthy volunteers as well as in patients who have received renal transplants have shown that St. John's wort interferes with absorption of tacrolimus.[58,59] Mycophenolic acid levels were not affected by St. John's wort in one of these studies.[59] The degree of interference was substantial, requiring a doubling of the usual dose to maintain therapeutic levels in the transplant patients. St. John's wort should not be combined with tacrolimus.

Conclusion

The calcineurin inhibitors cyclosporine and tacrolimus are widely used in patients who receive transplants and in people with severe autoimmune diseases. These drugs have substantial costs and adverse effects. Many natural products have been reported to enhance the drugs' efficacy and/or decrease their toxicity and should be considered potential adjuncts, with careful monitoring, in patients taking these drugs, par-

ticularly patients who experience adverse effects. Further research should be conducted to determine the optimal adjunct therapies with these promising herbs. A few herbs have been reported to interfere with these drugs and should not be combined with them. The current authors' article in the next issue will focus on other types of immunosuppressive drugs and their interactions with herbs. ■

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