Inhibitors of mTOR and FTY 720

Main Points

■ **Sirolimus** : The first representative of the inhibitors of mTOR (*rnammalian target of rapamycin),* sirolimus or rapamycin has dose-dependent secondary effects which are usually controllable. Sirolimus and tacrolimus appear to be combinable at therapeutic doses; the same is true of sirolimus and cyclosporine at moderate doses. The useful plasma concentrations of sirolimus vary from 5 to 20 ng/ml depending on the immunosuppressor combinations used. An ability of sirolimus to inhibit tumor proliferation and metastatic diffusion of a renal adenocarcinoma in the mouse has been described. Its complex effects on angiogenesis, fibrosis processes, and chronic rejection are being analyzed.

■ **Everolimus**: RAD or everolimus is a molecule with a short half-life, very close to sirolimus, but inducing fewer hematological effects. Regarding the therapeutic doses, it requires a circulating level of at least 3 ng/ml to prevent rejection; a level greater than 15 ng/ml increases the incidence of thrombopenia.

■ **FTY 720** : a new immunosuppressor agent, FTY 720 does not belong to any known family. It has a mode of action totally different from the immunosuppressors thus far available: by increasing, on the surface of the lymphocytes, the expression of a receptor of the chemokins, it allows them to be captured in the ganglions and secondary lymphoid organs, rendering them unavailable to the rejection reaction. Its half-life is very long (108 hours). Due to the features of its hepatic metabolism, the risk of drug interactions is very low.

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One session of the congress Transplantation 2001 was devoted to the use of sirolimus or rapamycin in kidney transplantation and another to that of new immunosuppressor agents

Sirolimus

Sirolimus is the premier representative of the inhibitors of mTOR ***(mammalian target of rapamycin***). Its secondary effects (thrombopenia, leucopenia, modifications of the lipid metabolism, etc.) are dose-dependent and usually controllable. But it remains to define its modes of administration and combination with the classical immunosuppressors.

Many therapy schemes have been tested, with or without calcineurin inhibitor (cyclosporine or tacrolimus). This latter combination seemed ill advised ***a priori*** on account of the fact that sirolimus and tacrolimus bind to the same intracellular protein, but with a risk of complications, something which has not been confirmed in the clinic at therapeutic doses.

Although sirolimus is not in itself nephrotoxic, its combination with cyclosporine appears to increase the risk of nephrotoxicity associated with this anti-calcineurin. Yet it is important to note that, in the majority of these studies, the circulating levels of cyclosporine were very high (on the order of 300 to 400 ng/ml), in the 2 branches studied. These various clinical trials on the combination thus often lead to a conclusion in favor of the halting of cyclosporine for the purpose of recovery of a normal kidney function in the transplanted subject, although this conclusion does not appear to be formally validated. In fact, it seems quite illogical to use sirolimus in combination with cyclosporine or tacrolimus at high doses since these 2 types of immunosuppressors have totally synergic effects in regard to their mode of action. Their combination at moderate dose can only be beneficial in terms of tolerance. Yet the efficacy of these therapy schemes remains to be proven.

One of the more interesting pieces of information during this session was given by Kahan [1] on the useful plasma levels of sirolimus, alone or in combination: he advises a target level of 15 ng/ml when sirolimus is used in monotherapy or at least without a calcineurin inhibitor, a level of 8 to 10 ng/ml when it is combined with cyclosporine in low dose, and a level less than or equal to 5 ng/ml in combination with high doses of cyclosporine. The useful plasma concentrations of rapamycin thus vary from 5 to 20 ng/ml depending on the immunosuppressor combinations used.

Some authors have used sirolimus in a secondary role, in order to diminish the nephrotoxic effects of cyclosporine, with not always convincing results. In fact, it appears that once the kidney function is deteriorated, with major histological lesions confirmed, the halting of cyclosporine and its replacement with sirolimus remains practically with no effect.

Other studies have tested sirolimus against cyclosporine in equally very large serum concentrations and producing lipid anomalies and arterial hypertension. In these therapy schemes, the lipid anomalies secondary to the administering of sirolimus remain more pronounced than under cyclosporine, but with no major statistical difference.

An exciting abstract (Breitenbuch, abst 549, p 250) described the ability of sirolimus to inhibit tumor proliferation and metastatic diffusion of a renal adenocarcinoma in the mouse, as compared to a control, unlike the highly stimulative effect of cyclosporine on tumor diffusion. This effect is accompanied by a limitation of angiogenesis and a lowering of othe circulating level of VEGF. This notion should be confirmed for other types of tumor and in human trials, but as of now the preferential use of sirolimus in transplanted neoplasic patients is worthy of consideration.

More generally, the complex effects of rapamycin on angiogenesis, fibrosis processes, and chronic rejection are being investigated. In an aortal graft model in the rat, at first in combination with cyclosporine, it limits the vascular lesions of chronic rejection but increases the expression of the genes of profibrotic cytokines, especially TGFß. In any case, it is not effective in rescue. On the other hand, it diminishes the proliferation of smooth muscle cells. This effect has already been utilized in cardiology, during the placement of stents coated with sirolimus, with very favorable results in terms of restenosis.

Thus, there is still a broad field for exploration. The interest of sirolimus needs to be evaluated in the long term, in reasonable protocols in event of combination with the anticalcineurins.

The new agents for maintenance of immunosuppression

This session was dedicated in part to RAD or everolimus, a molecule with a very short half-life, very similar to sirolimus but having the advantage of inducing fewer hematological effects, and in part to an original molecule, FTY 720.

Everolimus

Everolimus was studied in particular (Neoral®). This study involved 3 branches: the first with a dose of 0.75 mg x 2/day of everolimus, the second with a dose of 1.5 mg x 2/day of everolimus, the third with a dose of 2g/day of mycophenolate mofetil, all the patients furthermore receiving cyclosporine (Neoral®) in much more reasonable doses than in the trials with sirolimus [2] and corticoids. Everolimus has proven to be as effective as mycophenolate mofetil against acute rejection and graft loss, but at the price of lipid anomalies somewhat more pronounced and especially an increase in creatininemia at one year. Thus, everolimus may be viewed as a feasible alternative to sirolimus.

Another study [3] was devoted to defining the therapeutic zone of everolimus based on titration of the residual plasma concentrations in treated patients receiving 3 different dosages of the product taken in fixed and regular manner. The effective and non-toxic doses of everolimus were thus determined, after a treatment of 6 months, as a function of the residual levels and their correlations with the immunosuppressive efficacy and the secondary effects. It is also known that it requires a circulating level of at least 3 ng/ml of everolimus to prevent rejection and that a level greater than 15 ng/ml increases the incidence of thrombopenia.

FTY 720

This is a new immunosuppressor agent not belonging to any known family and having a totally different mode of action from the immunosuppressors available thus far. FTY 720 decreases the number of peripheral lymphocytes in reversible manner. It has no effect on apoptosis but increases, on the surface of the lymphocytes, the expression of a receptor of chemokins (CCR5) which allows a “capture” of the lymphocytes in the ganglions and secondary lymphoid organs, modifying the “homing” of the lymphocytes and thus rendering rejection.

The pharmacokinetics of FTY 720 has been tested in 16 patients with liver failure and an equal number of healthy volunteers [4]. FTY 720 administered orally has a very good digestive absorption with a concentration peak greatly spread out over time (on the order of 40 hours). Its half-life is very long, on the order of 108 hours, and its hepatic metabolism utilizes a subclass of cytochrome P 450 very seldom employed by known drugs, which gives it a very low risk of drug interactions. The elimination of the metabolites, which are biologically inactive, occurs principally by the urine. This molecule is used in a single dose with cyclosporine A. □

Text drafted by Marie Solignac based on information gathered from D. Morel, Hôpital Pellegrin, Bordeaux.

[References]

1. Kahan BO, Katz SM, Knight RJ. Outcome of 300 renal
transplant recipients treated de nova with a sirolimus cyclosporine regimen at a single center. AJT 2001 1 (supp l):abstract 145.
2. Vrtko R, Margreiter R, Weimar W et al The Rad 201
Study Group International, double-blind, parallel group
study of the safety and efficacy of Certican TM(RAD)
versus myocphenolate mofetil in combination with
Neoral® and steroids. AJT 2001 1 (suppl) :abstract 1337.
3. Kovarik JM, Rordorf C, McMahon L, Berthier S, Boger R
Exposure-response relationship for everolimus in
de novo renal transplantation: towards defning
a therapeutic range~ AJT 200 I 1(supp1):abstract 1336.
4. Barilla D, Choudhury S, Ledford P, Figueiredo J,
Schmauder R Effect of impaired hepatic function
on the systemic exposure of FTY 720 . AJT 200 I
I(suppl):abstract 1342.

MAIN POINTS

Inhibitors of mammalian target of rapamycin (mTOR)

■ **Sirolimus:** The leading member of the mTOR inhibitor family, sirolimus or rapamycin, has dose-dependent side effects that can generally be well controlled. Sirolimus can be combined with tacrolimus at therapeutic doses ; likewise for the sirolimus-cyclosporine combination at moderate dosage. Effective plasma concentrations of sirolimus vary from 5 to 20 ng/ml depending on the combination of immunosuppressant agents used. Sirolimus has been shown to inhibit metastatic diffusion of renal adenocarcinoma in the mouse. Its complex side effects on angiogenesis, fibro- sis processes and chronic rejection are still being investigated.

■ **Everolimus:** Everolimus, or RAD, has a very short half-life, but induces fewer hematology effects. The therapeutic dose must reach at least 3 ng/ml to prevent rejection. Doses above 15 ng/ml increase the risk of thrombocytopenia.

■ **FTY 720:** A new immunosuppressant agent, FTY 720, does not belong to any known family. It has a totally different mechanism of action compared with currently available immunosuppressants. FTY 720 increases the expression of chemokin receptors on the surface of T cells making them unavailable for the rejection reaction. FTY 720 has a very long half-life (108 hours). Due to its particular liver metabolism, there is a very low risk of drug interactions.

D. Morel

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That I possess advanced knowledge of the French and English languages. The attached French into English translation has been translated by me and to the best of my knowledge and belief, it is a true and accurate translation of: Les inhibiteurs de la, mTOR et le FTY 720

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