IMPACT OF CYP3A5 GENE POLYMORPHISM ON TACROLIMUS PHARMACOKINETICS IN KIDNEY TRANSPLANT PATIENTS

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Abstract

Nowadays in Kazakhstan there is an active development of organ transplantation, particularly kidney transplantation. The main purpose is not only to save as much lives as possible but also improve the survival rates of graft. In this way, now we are investigating personalization and rationalization of immunosuppressive treatment. In our country as in whole world genetic factors, determinating long-term graft survival, represent a great relevancy in transplantation. According to the results of clinical trial, there is a strict association between CYP3A5 (cytochrome P450) genetic polymorphism and tacrolimus pharmacokinetics. The determination of genetic polymorphism of CYP 3A5 gives us the opportunity to predefine the changes in blood concentrations of tacrolimus, better control of immunosuppressive therapy, that will positively affect the long-term graft survival.

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CYP3A5 генетикалық полиморфизмінің бүйрек реципиенттеріндегі такролимус фармакокинетикасына әсері

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Аңдатпа

Қазіргі танда Қазақстанда орган трансплантациясы, оның ішінде бүйрек трансплантациясы қарқынды түрде дамып келе жатыр. Негізгі мақсат көптеген науқастардың өмірін сақтап қалу ғана емес, трансплантаттің тірі қалу көрсеткіштерін жақсарту. Бұл жолда біз иммуносупрессивті емінің персонализация және рационализациясын зерттеп жатырмыз. Біздің мемлекетімізде және бүкіл дүниеде де трансплантаттың ұзақ мерзімде тірі қалуын анықтайтын генетикалық факторлар, трансплантологияда үлкен қызығушылық тудырып жатыр. Жасалған зерттеулердің нәтижелеі бойынша CYP3A5 (P450 цитохромы) генетическалық полиморфизмімен такролимустың фармакокинетикасы арасында нақты байланыс бар. CYP3A5 генетическалық полиморфизмін анықтау такролимус концентрациясының қандағы өзгерістерін алдын ала білу, иммуносупрессивті емді жақсырақ бақылау мүмкіншілігін тудырады және бұл трансплантаттың ұзақ мерзімде тірі қалу көрсеткштерін жақсартады.

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Түйін сөздер
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Влияние генетического полиморфизма CYP3A5 на фармакокинетику такролимуса у реципиентов почки

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Аннотация

На сегодняшний день в Казахстане идёт активное развитие трансплантации органов, в частности, пересадка почки. Главной целью является не только спасти как можно больше жизней, но и улучшить показатели выживаемости трансплантата. В этом направлении сегодня мы исследуем персонализацию и рационализацию иммуносупрессивно терапии. В нашей стране, как и во всем мире генетические факторы, детерминирующие выживаемость трансплантата в отдаленном периоде, предсталяет собой огромный интерес в трансплантологии. Согласно проведенным результатам имеется четкая связь между генетическим полиморфизмом CYP3A5 (цитохром P450) с фармакокинетикой такролимуса. Определение генетического полиморфизмам CYP3A5 позволит предопределить изменения концентрации такролимуса в крови, лучше контролировать иммуносупрессивную терапию, что положительно скажется на выживаемости трансплантата в отдаленном периоде.

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Ключевые слова
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Introduction

Nowadays kidney transplantation is the most preferable treatment option of terminal chronic kidney disease. The main advantage of kidney transplantation is that graft totally replaces the function of diseased kidney. Improvement of the quality of life of patients and return to their daily activities is another great advantage of this option.

With the improvement of donor selection, surgical technique and rational immunosuppressive treatment rates of short-term graft survival great increased. 1 – year graft survival from deceased donor is 95% whereas from living related donor is 98%. In Kazakhstan 1-year graft survival from living related donor is 91%. Despite these high indicators of 1-year graft survival, 5-year graft survival rates remain to be low. For example, in USA 5-year graft survival from decease donor is up to 80%, whereas from living donor is form 82 to 90 %, respectively. Thus, despite the improvement of short-term graft survival rates, long-term graft survival rates remain to be low [1].

So what lies under the graft loss in long-term period? It is thought to be that the main reason of graft loss in long-term period is so called graft nephropathy. The reasons of graft nephropathy are immunologic factors and, probably, genetic factors.

Recently there are many transplant centers where genetic factors and their influence of kidney graft function are investigated. In this way investigation of CYP3A5 genetic polymorphism, as a regulatory factor of tacrolimus pharmacokinetics is being more relevant.

Material and methods

We conducted a clinical trial, where we include 80 kidney recipients. Of them, 47 were male and 33 female patients. Mean age of patients was 43ұ4.1 years. All patients had been taking tacrolimus 0.1 mg/kg initially. Dose adjustment was by 1.0 mg a day up to target concentration (10-12 ng/ml). All patients were studied for CYP3A5 genetic polymorphism.

Results

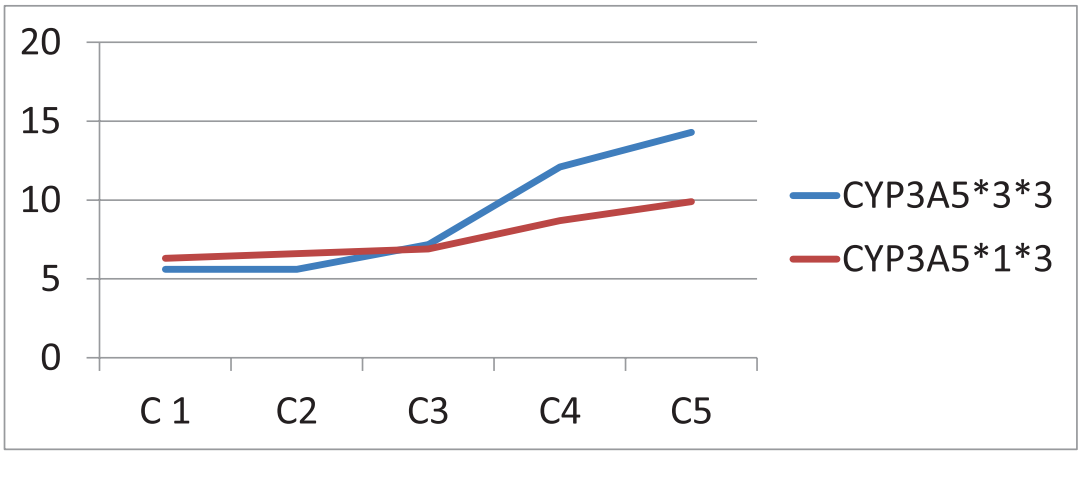
According to the received results 77 % of patients were CYP3A5*3 *3 homozygotes and the rest 33% were CYP3A5*1 *3 heterozygotes. Thus, first were classified as 1 group and the last as 2 group. At dose of 0.1 mg/kg in patients of both groups showed similar increase of tacrolimus level initially, but starting from the 2 week there was seen rapid increase of tacrolimus level in patients from the 1 group and dose adjustment was problematic due unpredictable course of concentration (Tab. 1). In patients from the 2 group tacrolimus concentration increased gradually without peaks and approximately at 2 weeks in postoperative period target concentration was reached. In contrast in patients form 1 group, at 2 weeks postoperatively we continued dose adjustment due to unpredictable rises and rapid falls of tacrolimus concentration.

Discussion

Fan B et al. studied pharmacokinetics of tacrolimus in patients taking prograf and advagraf [2]. 106 kidney transplant patients were included in this study. 61 of them had been taking prograf and 45 – advagraf. In 40% of patients there was low expression CYP3A5. In these patients target concentration of tacrolimus was reached at 21 day in advagraf group and 7 days in prograf group. 1-year graft survival was same in both groups. Infection was seen more frequently in patients taking advagraf.

Cheng et al. [3] studied 35 kidney recipients. Patients were divided in to 3 groups. First group were patients homozygote carriers of CYP3A5 (*1*1), the second group homozygote carriers of CYP3A5 (*3*3) and 3 group of patients heterozygotes of CYP3A5 (*1*3). Dose adjustment was performed after 7

Fig. 1.
Changes of tacrolimus concentration with CYP 3A5 genetic polymorphism



days, 1, 6 and 12 months postoperatively. Patients from the 1 group need high doses of tacrolimus in order to reach target concentration. There was high risk of graft rejection reaction in 1 group.

Similar results were received in clinical trial conducted by Quteineh L et al. [4] 136 kidney recipients were studied. As was in previous investigation patients with CYP3A5*1*1 genotype need higher doses of tacrolimus to reach the target concentration. Interestingly the situation remained the same for subsequent 6 and 12 months. CYP3A5 genetic polymorphism was not associated with tacrolimus nephrotoxicity but influenced the dose adjustment. Authors suggest preoperative evaluation of CYP3A5 genetic polymorphism, especially CYP3A5*1 carries.

Zhang X et al. [5] studied 118 kidney recipients. In CYP3A5*1*1 and *1*3 carriers tacrolimus concentration remained low even after dose adjustment in contrast to CYP3A5*3*3 carriers. For instance, half of patients with CYP3A5*1 after 7 days from initiation of immunosuppression tacrlimus was less than 5 ng/ml, whereas in CYP3A5*3 carriers tacrolimus concentration was more than 20 ng/ml. Thus this genetic factor is one of most important regulators of rational immunosuppressive treatment.

Conclusion

It is obvious from received results, that genetic polymorphism of CYP3A5 influences tacrolimus blood concentrations, that appears to be key factor in immunesupression [6]. Even in rational choice of dose of immunosuppressive agent, genetic factor must be considered as well. In order to improve long-term graft survival rates it is important to maintain therapeutic concentration of tacrolimus in blood. In this way in might important to determine the CYP3A5 genetic polymorphism preoperatively [7], as one of approved genetic determinants of graft survival. It is also important for the correct selection of initial dose.

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