SIGNIFICANCE OF DETERMINATION OF TACROLIMUS INTRAINDIVIDUAL VARIABILITY AND PHARMACOGENETIC MARKERS IN KIDNEY TRANSPLANT RECIPIENTS

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In the last three decades, a significant success was achieved in short-term outcomes after kidney transplantation, but it has not been followed with the same progress in long-term post-transplantation period. Long-term graft survival depends on genetic, immunological factors and patient-individualized immunosuppressive pharmacotherapy. Tacrolimus (Tac) is the backbone of the most immunosuppressive protocols after kidney transplantation nowadays and it is likely to be in a following decade. However, narrow therapeutic index and marked pharmacokinetic inter- and intra-individual variability complicate its clinical application. Therefore, therapeutic monitoring of Tac is necessary, but not sufficient to prevent graft rejection and/or the occurrence of adverse effects (renal dysfunction, hypertension, etc.). Cytochrome P450 (CYP) 3A5 6986A>G gene polymorphism is assumed to be a major determinant of interindividual pharmacokinetic variability of Tac. The carriers of functionally isoenzyme (expressers) require higher daily doses of Tac and have lower trough concentration in whole blood/daily dose ratio (C_0/D) of Tac compared to non-expressers (1). Given the inconsistency of the results regarding CYP3A5 effect on long-term post-transplantation outcomes, the investigation of new pharmacogenetic biomarkers could be of great importance. A growing number of studies have been focused on the association of interindividual and/or intraindividual variability of Tac exposure in the first post-transplantation year with adverse outcomes in later periods (e.g. late acute rejection, chronic dysfunction, rejection and graft loss) (2). The introduction of CYP3A5 genotyping into clinical practice, simultaneously with the assessment of Tac C_0/D and intraindividual variability may categorize patients towards risk of graft function deterioration in long-term post-transplantation period.

References

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ZNAČAJ ODREĐIVANJA INTRAINDIVIDUALNE VARIJABILNOSTI TAKROLIMUSA I FARMAKOGENETIČKIH MARKERA KOD PACIJENATA SA TRANSPLANTIRANIM BUBREGOM

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U protekle tri decenije ostvaren je značajan uspeh u kratkoročnim ishodima nakon transplantacije bubrega, ali bez istovetnog napretka u dugoročnom post-transplantacionom periodu. Dugoročno preživljavanje grafta zavisi od genetičkih, imunoloških faktora i imunosupresivne farmakoterapije prilagođene pacijentu. Takrolimus (Tac) je okosnica većine imunosupresivnih protokola nakon transplantacije bubrega danas, a verovatno će ostati i u narednoj deceniji. Međutim, mali terapijski indeks i izražena farmakokinetička inter- i intraindividualna varijabilnost komplikuju njegovu kliničku primenu. U skladu s tim, terapijski monitoring Tac je neophodan, ali ne i dovoljan u cilju prevencije odbacivanja grafta i/ili pojave neželjenih efekata (renalna disfunkcija, hipertenzija i dr.). Citohrom P450 3A5 (CYP3A5) 6986A>G genski polimorfizam se smatra glavnom determinantom interindividualne farmakokinetičke varijabilnosti Tac. Naime, nosioci funkcionalno aktivnog izoenzima (ekspresori) zahtevaju veće dnevne doze Tac i imaju nižu vrednost odnosa minimalne koncetracije u punoj krvi i dnevne doze (C_0/D) Tac u poređenju sa neekspresorima (1). S obzirom na nedoslednost rezultata ispitivanja efekta CYP3A5 na post-transplantacione ishode, istraživanje novih farmakogenetičkih biomarkera može biti od velikog značaja. Veliki broj istraživanja usmeren je na ispitivanje povezanosti parametara interindividualne i/ili intraindividualne varijabilnosti u izloženosti Tac u prvoj godini nakon transplantacije sa nepovoljnim ishodima u kasnijim periodima (npr. kasno akutno odbacivanje, hronična disfunkcija, hronično odbacivanje i gubitak grafta) (2). U skladu s tim, uvođenje CYP3A5 genotipizacije u kliničku praksu, istovremeno sa procenom C_0/D i intraindividualne varijabilnosti Tac može omogućiti kategorizaciju pacijenata prema riziku pogoršanja funkcije grafta u dugoročnom post-transplantacionom periodu.

Literatura

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