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SIGNIFICANCE OF SIMULTANEOUS ANALYSIS OF CYP3A5 GENOTYPE, CONCENTRATION/DOSE RATIO AND INTRAINDIVIDUAL VARIABILITY OF TACROLIMUS IN KIDNEY TRANSPLANT RECIPIENTS

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Tacrolimus (Tac) is a backbone of the most immunosuppressive protocols after kidney transplantation (Tx), but it is characterized by large inter- and intraindividual (IPV) variability in pharmacokinetics and exposure. It has been assumed that low Tac dose-adjusted through concentration (C_0/D), which corresponds with a faster metabolism and lower bioavailability, and high Tac IPV within the first post-transplantation year may be associated with kidney graft impairment or loss in the late period after Tx (1,2). This study aimed to estimate the individual and/or combined effect of Tac IPV and mean C_0/D during 6-12 months post-transplantation on estimated glomerular filtration rate (eGFR) or composite endpoint [graft failure, chronic allograft dysfunction, chronic rejection and doubling of serum creatinine concentration] in the period between 13 and 36 months after Tx. In addition, the goal was to analyze the impact of cytochrome P450 (CYP) 3A5 genotype on interindividual variability of Tac exposure within the entire study period. The study enrolled 104 kidney transplant recipients and included 2541 patient examinations up to 3 years after Tx. Tacrolimus IPV was calculated as the coefficient of variation of the Tac C_0/D between 6 and 12 months after Tx. Patients were divided into groups based on the Tac IPV tertiles (low, middle and high IPV) and the median value of mean C_0/D during 6-12 months post-transplantation (low and high C_0/D). All patients were genotyped on CYP3A5 6986A>G gene polymorphism. Linear regression analysis showed that the eGFR in the late period after Tx may be independently affected by Tac IPV, mean Tac C_0/D during 6-12 months post-transplantation, acute rejection and kidney function in the early post-transplantation period. In addition, the patients characterized by high IPV/low C_0/D had significantly lower eGFR between 13th and 36th month after Tx compared to the other groups (high IPV/high C_0/D, low+middle IPV/low C_0/D, low+middle IPV/high C_0/D) ($p<0.001$). The performed Kaplan-Meier analysis did not show an individual association between Tac IPV or Tac C_0/D with the composite endpoint. Still, the patients in the combined high IPV/low C_0/D group had significantly reduced graft survival compared to the other patient groups ($p=0.035$). The carriers of CYP3A5*1/*3 genotype had lower C_0/D compared to the CYP3A5*3/*3 carriers during the entire study period ($p<0.01$). The simultaneous assessment of CYP3A5 genotype, in the context of Tac C_0/D prediction, and Tac IPV could be additional help to categorize patients towards the risk of graft deterioration in the long-term post-transplantation period.

References

1. Shuker N, van Gelder T, Hesselink DA. Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. Transplant Rev. (Orlando). 2015; 29:78-84.
2. Jouve T, Fonrose X, Noble J, et al. The TOMATO Study (Tacrolimus Metabolization in Kidney Transplantation): Impact of the Concentration-Dose Ratio on Death-censored Graft Survival. Transplantation. 2020;104:1263-1271.

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ZNAČAJ ISTOVREMENE ANALIZE GENOTIPA CYP3A5, ODNOSA KONCENTRACIJA/DOZA I INTRAINDIVIDUALNE VARIJABILNOSTI TAKROLIMUSA KOD PACIJENATA SA TRANSPLANTIRANIM BUBREGOM

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Takrolimus (Tac) je osnova većine imunosupresivnih protokola nakon transplantacije bubrega (Tx). Međutim, njega karakteriše izražena inter- i intraindividualna (IPV) varijabilnost u farmakokinetici i izloženosti. Pretpostavlja se da niska vrednost koncentracije Tac prilagođene dozi (C_0/D), koja odgovara bržem metabolizmu i nižoj bioraspoloživosti, i visoka Tac IPV u prvoj post-transplantacionoj godini mogu biti povezane sa oštećenjem ili gubitkom grafta u kasnijem periodu nakon Tx (1,2). Ova studija je imala za cilj da proceni pojedinačni i/ili kombinovani efekat Tac IPV i srednje vrednosti C_0/D tokom 6-12 meseci nakon Tx na procenjenu brzinu glomerularne filtracije (eGFR) ili nastanak neželjenih post-transplantacionih ishoda [smanjena funkcija grafta, hronična disfunkcija grafta, hronično odbacivanje grafta i dupliranje koncentracije serumskog kreatinina] u periodu između 13 i 36 meseci nakon Tx. Osim toga, cilj je bio analiza uticaja genotipa citohrom P450 (CYP) 3A5 na interindividualnu varijabilnost u izloženosti Tac tokom celokupnog perioda trajanja studije. Studija je uključila 104 pacijenata sa transplantiranim bubregom i obuhvatila je 2541 pregleda pacijenata u periodu od 3 godine nakon Tx. Takrolimus IPV izračunat je kao koeficijent varijacije Tac C_0/D između 6 i 12 meseci nakon Tx. Pacijenti su podeljeni u grupe na osnovu tercila Tac IPV (nizak, srednji i visok Tac IPV) i medijane srednje vrednosti C_0/D tokom 6-12 meseci nakon Tx (nizak i visok Tac C_0/D). Svim pacijentima je određen polimorfizam 6986A> G na genu za CYP3A5. Linearna regresiona analiza je pokazala da Tac IPV, srednja vrednost Tac C_0/D tokom 6-12 meseci, akutno odbacivanje i funkcija bubrega u ranom post-transplantacionom periodu mogu nezavisno uticati na eGFR u kasnijem periodu nakon Tx. Osim toga, pacijenti koje karakteriše visok IPV/nizak C_0/D imali su značajno niži eGFR između 13. i 36. meseca nakon Tx u poređenju sa ostalim grupama (visok IPV/visok C_0/D, nizak+srednji IPV/nizak C_0/D, nizak +srednji IPV/visok C_0/D) ($p<0,001$). Sprovedena Kaplan-Meier analiza nije pokazala pojedinačnu povezanost između Tac IPV ili Tac C_0/D sa neželjenim post-transplantacionim ishodima. Ipak, pacijenti u kombinovanoj grupi visok IPV/nizak C_0/D imali su značajno smanjenje preživljavanja grafta u poređenju sa drugim grupama pacijenata ($p=0,035$). Nosioci genotipa CYP3A5*1/*3 imali su niži C_0/D u poređenju sa nosiocima CYP3A5*3/*3 genotipa tokom celokupnog perioda trajanja studije ($p<0,01$). Istovremena procena genotipa CYP3A5, u kontekstu predviđanja Tac C_0/D, i Tac IPV može predstavljati dodatnu pomoć u cilju kategorizacije pacijenata prema riziku od pogoršanja funkcije grafta u dugoročnom periodu nakon Tx.

Literatura

1. Shuker N, van Gelder T, Hesselink DA. Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. Transplant Rev. (Orlando). 2015; 29:78-84.
2. Jouve T, Fonrose X, Noble J, et al. The TOMATO Study (Tacrolimus Metabolization in Kidney Transplantation): Impact of the Concentration-Dose Ratio on Death-censored Graft Survival. Transplantation. 2020;104:1263-1271.

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