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Commentary

Characteristics of Tacrolimus in Lung Transplant Recipients

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DESCRIPTION

Tacrolimus is a potent calcineurin inhibitor that is routinely used to prevent lung transplant rejection and is an important component of immune maintenance therapy. Tacrolimus outperforms other immunosuppressive agents in terms of efficacy and safety in lung transplant recipients, and it is frequently used in combination with mycophenolic acids and glucocorticoids, which is the cornerstone drug of the immunosuppressive regimen following lung transplantation.

Tacrolimus' therapeutic window is small, and individual variation is significant, limiting its clinical utility. The limited therapeutic window affects the efficacy and safety of anti-rejection medication after lung transplantation. Inadequate drug concentration increases the chance of rejection, whereas high drug concentration can lead to complications such as infection and renal failure. Tacrolimus outperforms other immunosuppressive medications in terms of efficacy and safety in lung transplant recipients and is frequently used in combination with mycophenolic acids and glucocorticoids, which is the cornerstone drug of the immunosuppressive regimen after lung transplantation.

However, the therapeutic window of tacrolimus is narrow, and individual variation is high, limiting its clinical applicability. The restricted therapeutic window has an impact on the efficacy and safety of anti-rejection therapy after lung transplantation. Inadequate drug concentration increases the likelihood of rejection, whereas excessive drug concentration may result in adverse outcomes such as infection and renal failure.

Tacrolimus pharmacokinetics varies greatly between individuals. Tacrolimus blood levels are highly unstable and variable due to a range of confounding factors such as hereditary factors, pathophysiological factors, and combination medicine, making it challenging for doctors to create suitable customized dose regimens. TDM is based on the association between tacrolimus blood concentration and clinical efficacy, which provides a quantitative basis for tacrolimus dosage adjustment and is a crucial technique for transplantation centers to create customized regimens. Within the first three months after lung transplantation, the whole blood trough concentration of tacrolimus is regularly measured within the suggested range of 10-15 mg.

Although tacrolimus TDM is commonly utilized in the clinic, it has several drawbacks. First, there is still a dearth of reliable evidence from vast clinical trials or authoritative guidelines, which now mostly refer to those of other solid organ transplantation populations. Furthermore, cardiopulmonary function is unstable in the early stages following lung transplantation, and various organs undergo varying degrees of ischemia and hypoxia during operation, paired with organ failure, leading in substantial changes in tacrolimus trough concentration.

In contrast, *CYP3A5* is the major metabolic enzyme of tacrolimus, and it has a considerable impact on its metabolism. There is, however, a gene polymorphism at this locus. Many investigations have found that the *CYP3A5*3* polymorphism has a considerable effect on tacrolimus blood levels. According to the Clinical Pharmacogenetics Implementation Consortium, individuals with extensive and medium metabolism should take 1.5-2 times the normal dose. The mutation rate of the *CYP3A5*3* gene varies greatly between ethnic groups, with Asians having the highest mutation rate of 74.2%. Even if the dosage is calculated based on the *CYP3A5* polymorphism, TDM is still required for dosage adjustment due to the pharmacokinetic properties of tacrolimus and the influence of concomitant medications.

Tacrolimus pharmacokinetics differs between patients with cystic fibrosis and those without. Many factors, including *CYP3A5*3* genotype, main disease, haematocrit, body weight, and concurrent medication, influence tacrolimus clearance rate, resulting in individual variances in blood concentration. According to the findings of the preceding investigations, the blood content of tacrolimus fluctuates significantly after lung transplantation. Further research on the factors that impact individual variability in tacrolimus after lung transplantation is required.

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