Leflunomide Therapy in Kidney Transplantation: Ready for Prime Time?

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K polyomavirus has become a scourge in kidney transplantation, mediating graft loss with progressive tubular cell death and interstitial inflammation and fibrosis (1). In the setting of immunosuppression, the virus reactivates, replicating along the tubular epithelium, spreading to other uninfected tubules, entering the tubular lumen after cell lysis, and eventually entering the bloodstream through destruction of peritubular capillaries (2). Whereas viruria is common, viremia occurs in only 13% of recipients, and nephropathy in 8% (3). Once a diagnosis is established by transplant biopsy and viral load measurements, the primary treatment strategy is immunosuppressive withdrawal (4). Disease that is more fully progressed may be unresponsive to any manipulation. Adjuvant therapies have included intravenous immune globulin, quinolones, and cidofovir, all with varying results (5). Center-specific experiences have been reported, but there are no definitive treatments.

Leflunomide is an immunosuppressive agent approved for use in rheumatoid arthritis. Metabolized by the liver, the active metabolite A77 1726 blocks tyrosine kinase activity as well as pyrimidine synthesis. Leflunomide also has antiviral activity against cytomegalovirus replication in vitro and in rodent models. Although limited, initial experience in kidney transplant recipients demonstrated significant interpatient variability in drug levels and anemia while facilitating calcineurin inhibitor withdrawal (6). Based on this immunosuppressive profile and the potential to halt BK activity, leflunomide has entered into practice for BK nephropathy. The initial report in 17 kidney transplant recipients in place of mycophenolate dem- 

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total DNA copy number measured by polymerase chain reaction, the effective concentration 50 (EC50; drug concentration in which viral load is reduced by 50%) is 11.3 ± 2.8 μg/ml (~40.7 μM) with a 50% inhibitory concentration (IC50) measured as a 50% reduction in housekeeping gene expression is 39.7 ± 6.9 μg/ml (~147 μM), resulting in a relatively low selectivity index of 3.8 ± 0.8 (12). Similar semiquantitative measurements using immunofluorescence of late viral protein VP-1 suggest an IC50 of 40 μM (8). However, more robust quantitative methodologies using hemagglutination or virion quantitation by in situ hybridization (13) have not been undertaken. With the broad range of effects of this drug, we need to more completely understand the specific mechanisms of its antiviral activity. The onus is now on our community to derive better strategies, be they direct antiviral agents or indirect strategies of immune monitoring, to intercept infection before full disease manifestation.

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Disclosures
None.

References

See related article, “Higher Levels of Leflunomide Are Associated with Hemolysis and Are not Superior to Lower Levels for BK Virus Clearance in Renal Transplant Patients,” on pages 829–835.