

The Pharmacokinetics of Pegylated Interferon in Renal Disease

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It has been generally accepted that the kidney is the main site of nonpegylated interferon alpha (IFN alpha) catabolism/elimination (1). These molecules are filtered through the glomeruli by luminal endocytosis and during proximal tubular reabsorption undergo proteolytic degradation. This proposed pathway of clearance of IFN alpha is largely based on animal studies (2) with the limited studies in humans being somewhat conflicting. An early study of recombinant IFN alpha pharmacokinetics (PK) in patients on hemodialysis receiving 2 doses of 3 million IU interferon alfa-2a suggested that ESRD and hemodialysis do not alter the PK properties of lower dose exogenous IFN alpha (3). In contrast, a more detailed multiple dose study of higher doses of IFN alpha in a similar patient population reported a significant increase in the elimination half-life of IFN alfa-2b (6.0 vs. 10.0 hours), increased serum levels of IFN and increased areas under the time-concentration curves in patients with ESRD versus nonuremic patients (4). Overall the data would appear to indicate that in humans approximately 65-80% of the clearance of nonpegylated IFN alpha is via renal mechanisms.

Similar to the situation for nonpegylated IFN alpha, there is currently limited data available for the precise effect of renal impairment on the PK of pegylated IFN alpha. The situation for pegylated IFN alpha is complicated by the fact that the size of the pegylated molecule may have a major impact on tissue distribution and catabolism/elimination. Mass balance studies of appropriately labeled pegylated IFN alpha will be extremely difficult to do in humans and have not been reported to date. An animal study of peginterferon alfa-2a, which consists of a 40 kDa branched-chain polyethylene glycol molecule attached to a molecule of IFN alpha, has reported the clearance of the intact molecule predominantly occurs in non-renal sites with the liver being an important site of elimination, perhaps based on its higher relative allocation of total body blood flow (5). Complimenting this animal study, a clinical study of patients with varying degrees of renal impairment down to a creatinine clearance of 20 ml/min, suggests that the PK properties of peginterferon alfa-2a are not altered by this degree of renal impairment (6). An additional study of peginterferon alfa-2a in volunteers with ESRD has demonstrated a 25-45% reduction in apparent total body clearance in these individuals, further supporting the suggestion that in contrast to nonpegylated IFN alpha, renal elimination accounts for a smaller proportion of total apparent clearance of peginterferon alfa-2a (7). This data, including the observed safety profile, suggests that the dose of peginterferon alfa-2a may require no or minimal adjustment in patients with ESRD. The situation for peginterferon alfa-2b, which consists of a 12 kDa polyethylene glycol molecule attached to a molecule of IFN alpha, may also be similar with the apparent clearance of that compound attributable to renal elimination being reported as approximately 30% based on a study of subjects with varying degrees of renal dysfunction (data on file, Schering-Plough Research Institute, Kenilworth, NJ).

References

1. Wills RJ. *Clinical pharmacokinetics of interferons*. *Clin Pharmacokinet* 1990; 19: 390-399.
2. Bino T, Madar Z, Gettler A, Rosenberg H. *The kidney is the main site of interferon degradation*. *J Interferon Res* 1982; 2:301-308.
3. Hirsch MS, Tolckoff-Rubin NE, Kelly AP, Rubin RH. *Pharmacokinetics of human and recombinant leucocyte interferon in patients with chronic renal failure who are undergoing hemodialysis*. *J InfDis* 1983; 148: 355.
4. Uchihara M, Izumi N, Sakai Y, et al. *Interferon therapy for chronic hepatitis C in hemodialysis patients: increased serum levels of interferon*. *Nephron* 1998; 80: 51-56
5. Modi MW, Fulton JS, Buckman DK, et al. *Clearance of pegylated (40 kDa) interferon alfa-2a Pegasys is primarily hepatic*. *Hepatology* 2000; 32(Suppl.Pt. 2): 910A
6. Martin P, Mitra S, Farrington K, et al. *Pegylated 40 kDa interferon alfa-2a Pegasys is unaffected by renal impairment*. *Hepatology* 2000; 32 (Suppl.Pt.2):370
7. Lamb M, Marks IM, Modi MW, et al. *Peginterferon alfa-2a 40 kDa Pegasys can be administered safely in patients with end-stage renal disease*. *Hepatology* 2001; 34(Suppl.Pt.2):190