measured GFR. A simple equation predicting GFR from Scr and LM, that can be correctly assessed in renal insufficient patients without DEXA, simply from anthropometrics or body impedance analysis [3], would constitute important progress for practice. However, the relationships between LM and creatinine production, and between Scr and glomerular filtration, are not simple. The formula proposed by Taylor et al. [1] leads to an important overestimation of GFR for our diabetic patients. As mentioned by the authors, further work is also needed to validate this formula on a higher number of non-diabetic subjects, with Scr lower than 3.2 mg/dl.

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Reply

Sir,

We would like to thank the authors for their interest in our study. We previously published a formula that predicts GFR simply by using measurements of lean mass and serum creatinine. The investigators in this study state that our formula overestimated GFR when calculated using data from 54 diabetic patients. The authors make a valid point that

<table>
<thead>
<tr>
<th>Measured GFR</th>
<th>Correlation with measured GFR</th>
<th>Difference with measured GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD</td>
<td>40±13 r = 0.80, P &lt; 0.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Cockcroft</td>
<td>43±16 r = 0.48, P &lt; 0.001 NS</td>
<td></td>
</tr>
<tr>
<td>Taylor et al. [1]</td>
<td>51±25 r = 0.63, P &lt; 0.0001 P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

GFR becomes negative with creatinines above 3.2 mg/dl. Our subjects did not have GFRs under 31 ml/min or serum creatinines above 2.4 mg/dl and it is possible that we only reported on the linear portion of this relationship and that the line may actually be curvilinear at the lower end, as GFR decreases and creatinine increases. However, our study focused on non-diabetic subjects with a broad range of GFRs, as opposed to diabetics with much lower renal function. Our formula may still be more accurate than the MDRD for certain groups, as it has been reported that the MDRD formula is less accurate in subjects with higher GFRs and normal renal function [1,2]. It is also important to note that some variability between the two datasets could have been introduced, due to the differences in the methods for measuring GFR (51Cr-EDTA vs 125-I iothalamate), as well as potential differences in technique with the measurement of lean mass by DEXA scan and serum creatinine. Despite differences in the results of these two studies, we do appreciate the fact that these investigators tested and challenged our findings. Again, further study should be devoted to this subject, in order to conclusively establish a simplified calculation to represent this potentially complex relationship.

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Pegylated interferon and ribavirin in haemodialysis patients

Sir,

Recently Russo et al. [1] reported a randomized study of sixteen haemodialysis patients with chronic hepatitis C virus infection (HCV), treated with pegylated interferon-alpha-2b. They concluded that its use was poorly tolerated and associated with substantial side-effects in their study. Two study-arms randomized patients to pegylated interferon-alpha-2b 1.0 g/kg or 0.5 g/kg per week. Only three subjects had a 24-week treatment response and two of these had a sustained viral response after the termination of therapy, all in the 1.0 g/kg group.

Standard therapy today for patients with HCV is long-acting pegylated interferon and ribavirin. Until recently, there has been little experience with either drug in end-stage renal disease (ESRD). Sustained viral responses with the use of interferon-alpha has been reported, in a number of both controlled and uncontrolled studies, to vary between 16 and 64% with the lowest response rate in the difficult to treat HCV genotypes i.e genotype 1. However, tolerance issues are common with at least 30% never completing therapy [2,3]. Pegylated interferons are currently available as peg-alpha-2a
(Pegasys® 40 kDa; Roche Diagnostics) or peg-alpha-2b (PegIntron® 12 kDa; Schering-Plough), the former reported to have a large metabolic clearance compared with a higher degree of renal clearance for the latter.

We have previously published treatment studies in both dialysis patients as well as in patients with reduced renal function with HCV infection [4,5]. A high performance liquid chromatography (HPLC) method was developed to measure ribavirin in plasma based on patients with normal renal function, which enabled the use of ribavirin together with interferon in renal insufficiency.

In a more recent article, we used pegylated interferons with ribavirin in dialysis patients [6]. Six haemodialysis patients were treated with peg-alpha-2b (n = 4) and peg-alpha-2a (n = 2) for 24–48 weeks according to HCV genotype, with a dose of 50 or 135 μg/week, respectively. All but one patient had difficult to treat HCV genotypes. The dose selected for peg-alpha-2b was reduced by 25–30% from the dose of 1 μg/kg/week, because of its larger renal elimination, which in most patients was equivalent to 0.7 μg/kg. Peg-alpha-2a was reduced to 135 μg according to the recommendation from the manufacturer for patients with a creatinine clearance of <20 ml/min. As in previous studies, patients were given reduced ribavirin doses and were subsequently monitored with ribavirin plasma concentration aiming at a target concentration of 10–15 μmol/l. Average ribavirin dose was 170–300 mg/day.

All patients became HCV-RNA-PCR negative during treatment, which was completed or nearly completed in four patients.

Ribavirin-induced anaemia was treated with high doses of erythropoietin and low doses of iron. Blood transfusions were not needed. Interferon related side-effects such as initial flu-like syndrome, myalgia and fatigue were common. In one patient peg-alpha-2b was permanently reduced to 50 μg every 9–10 days with improvement in tolerance. In spite of this reduction, this patient attained a sustained viral response. One patient terminated therapy prematurely due to pronounced interferon related side-effects and another died of myocardial infarction, probably not related to therapy. Three patients have remained HCV-RNA negative with extended follow-up, two of whom have subsequently had a successful kidney transplant.

As mentioned by Russo et al. [1], the dosing of peginterferon might have been inadequate in their study; possibly the lower dose was too low for any effect and the higher dose associated with more side-effects. The poor outcome could in addition be due to difficult to treat HCV genotypes and the fact that a substantial number of patients in the study were African-Americans who have lower response rates. The degree of liver damage was also fairly advanced in many patients, which is generally a negative predictor for treatment outcome. Finally, interferon monotherapy, both the pegylated and unpegylated forms, clearly has limitations. Combination therapy with ribavirin as in our experience, and possibly future ribavirin analogues associated with less anaemia or protease inhibitors currently undergoing clinical trials, are likely to contribute to better efficacy, also in ESRD.

The authors also recommend administering peginterferon on the off-dialysis day. The reasons for this are somewhat unclear. For practical reasons, we have given the patient the injection at the end of the dialysis session without any side-effects other than those to be expected with interferon therapy in general.

Pegylated interferons are, in our opinion, likely to become a valuable addition for HCV therapy in ESRD and are possible to combine with ribavirin. However, we would favour prospective pharmacokinetic and tolerability studies of both peg-alfa-2a and 2b before definite dosing recommendations can be made.

Conflict of interest statement. The authors have conducted research sponsored by Schering-Plough and Roche.


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Reply

Sir,

Bruchfeld et al. raise important issues regarding the treatment of dialysis patients with hepatitis C, including the role of ribavirin as part of the antiviral regimen. There is no doubt that the addition of ribavirin to interferon certainly results in improved efficacy, but it may be at the expense of increased side effects in dialysis patients. Ribavirin could be potentially dangerous in dialysis patients, at least partly due to increased haemolysis. The authors state that they have successfully used ribavirin in this patient population with acceptable safety. The evidence they provide for this are three small studies, each including 6 or 7 patients [1–3]. The most recent study was a retrospective analysis of six dialysis patients with hepatitis C, treated with either pegylated interferon alpha-2a.

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