ated with a higher incidence of distant recurrences than was the use of internally cooled electrodes (Covidien). We had also shown in a pilot study that by using multipolar electrodes (Celon), complete ablation of tumors larger than 5 cm could be frequently achieved, a result out of reach of monopolar electrodes.[2] Therefore, the use of a multipolar device for the treatment of smaller tumors such as those treated in our study might have reduced local recurrence rate. The heterogeneity of the techniques used is inherent to the retrospective nature of our study and the improvement of results with time following improvement in experience and technology is shared by other types of treatments such as surgery. This phenomenon needs to be stressed, because the overall results reported are likely to be less favorable than those expected today with RFA using up-to-date technique and technology.

4. From our point of view, matching patients subjected to a curative treatment like RFA with those having usually more advanced HCC and treated by a palliative one (e.g., chemoembolization) would make little sense. Comparing survival after RFA in patients who were eligible for resection with those for whom resection was contraindicated, we found a huge difference between the two groups in terms of 5-year overall survival rates (76% versus 27%, respectively). This result confirms that criteria usually used to select patients with HCC for resection (e.g., Barcelona Clinic Liver Cancer criteria) strongly affect survival of patient, whatever the type of treatment attempted (resection or RFA). In addition, the 76% for 5-year overall survival rate obtained with RFA in patients potentially eligible for resection is favorably comparable with those reported in surgical series. Therefore, we conclude that the indication of RFA as first-line treatment even for patients usually considered as good candidates for surgery was justified regarding its far lower complication rate and its repeatability in case of recurrence. Nevertheless, there is probably a subgroup of patients in whom RFA, although potentially curative, had little chance to achieve its goal: for example, patients with three tumors or who had an even limited vascular invasion. The reduced number of cases responding to this category did not allow us any case-control comparison with chemoembolization.

We thank the authors of the letter to have helped us clarify these points.

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Metformin, Hepatitis C, and Insulin Resistance: Sufficient Evidence?

To the Editor:

The prospective, multicentered, randomized, double-blinded, placebo-controlled trial by Romero-Gómez and coworkers[1] demonstrating that adding metformin to peginterferon and ribavirin was safe and improved insulin sensitivity in treatment-naïve patients without diabetes who are chronically infected with genotype 1 hepatitis C virus (HCV) raises a number of issues.

First, the cutoff used for insulin resistance in this study (i.e., HOMA [homeostasis model assessment] index > 2) was somewhat low, and the reasons behind this choice are not sufficiently explained by the authors. In clinical research, the decision on what cutoff points to use is crucial to give optimal enlightenment of individuals in need of pharmacological interventions because of increased insulin resistance. This choice must be made by considering the overall impact on health due to intervention (e.g., improvement of insulin resistance) and potential burden of overtreatment if a low cutoff point is employed. Second, the analysis by Romero-Gómez et al. is limited to patients with genotype 1 chronic hepatitis C. Because insulin resistance in patients with chronic hepatitis C does not differ among HCV genotypes,[2] the reasons for this strict inclusion criteria is not sufficiently elucidated. Third, serum HCV RNA levels do not seem to predict insulin resistance in patients with chronic hepatitis C,[2] and thus it is unclear whether the increased viral decline as seen in the metformin arm is the cause of improved HOMA values. Finally, the positive effects of metformin on sustained virological response and viral decline were confined to female patients. Notably, these findings were mainly derived from a sex-based subgroup analysis. Meaningful information from subgroup analyses within a randomized trial is restricted by low statistical power and the issue of multiple testing. In order to minimize the risk of accepting and publishing false positives, it has been proposed that the results of subgroup analysis be accepted merely as hypotheses.[3] Given the risks of false positive findings when multiple subgroup analyses are done, it is not surprising that a subgroup-specific test may show a significant ($P < 0.05$) or suggestive ($P = 0.05$ to $P = 0.10$) effect of treatment, even when the trial failed to do so overall.[3,4] Of note, this is exactly the case of the study by Romero-Gómez et al.[1] In order to support the validity of a claimed subgroup effect, there are some potential strategies, including the availability of a biological explanation (that is clearly missing in the published trial) or replication in another independent study.[3] Taken together, the evidence published by Romero-Gómez et al. is likely insufficient to guide clinical care in patients with chronic hepatitis C who have insulin resistance.

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Reply:

We thank the authors for their interest in our article[1] on treatment of insulin resistance in patients with hepatitis C virus (HCV) infection. The authors make several points that require addressing. First, "the choice of a cutoff for HOMA > 2 could be somewhat low". We elected this cutoff based on our previous results[2] showing that a homeostasis model assessment (HOMA) score > 2 had a significant, and independent, negative impact on the sustained virological response (SVR) rate. These results encouraged us to include this subpopulation in the present study. Second, "the inclusion was limited to patients with genotype 1" infection. Currently, there is a need to increase therapeutic efficacy in patients infected with genotype 1. They represent the most prevalent genotype, and in which we had demonstrated a negative impact of baseline insulin resistance on SVR.[2] Studies addressing the impact of treating insulin resistance in other genotypes are urgently required. Third, "the relationship between insulin resistance and HCV replication is controversial". In our study, viral decline during the first 12 weeks was higher in females receiving metformin, and was related to better SVR rate. These findings support the hypothesis that metformin works better in females by improving antiviral activity of peginterferon plus ribavirin. Fourth, "sex-based subgroup analysis". Despite sex-based subgroup analysis having not been an "*a priori*" issue in the study plan, the distribution of the variables included in the model would probably not change even when increasing the sample size and, as such, the significant difference induced by metformin would be maintained. The statistical power of analysis of the cohort of females is shown in Fig. 1. (nQuery Advisor 4.0; Statistical Solutions, Saugus, MA). Indeed, women were not underrepresented in this trial, because there was no significant differences in sex distribution in the studied population sample which, in all respects, reflects the overall distribution of hepatitis C prevalence by sex in Spain.[3] The impact of sex on SVR was evaluated using the chi-squared test in the univariate analysis and in the multivariate logistic regression analysis. Interactions need to be studied between independent variables, but lack meaning if applied to an independent versus a dependent variable.[4]

Although our trial was not designed to evaluate potential sex differences, a potential type-2 error plus the power analysis and the doubled SVR in females receiving metformin prompted our hypothesis that metformin improves antiviral efficacy of treatment with peginterferon alfa-2a plus ribavirin. We do agree, however, that confirmatory studies of this novel finding are warranted.

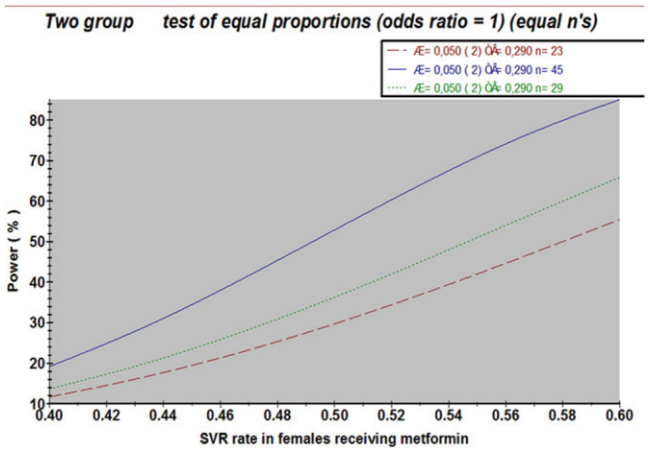

Figure 1. Calculation of statistical power according to sustained virological response rate in three cohorts of females.

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