

## CCR Translations

Commentary on Lee et al., p. 3188

## Serum Cholesterol and mTOR Inhibitors: Surrogate Biomarker or Epiphenomenon?

Daniel C. Cho<sup>1</sup> and Michael B. Atkins<sup>2</sup>

Lee and colleagues report that increase in serum cholesterol is associated with improved clinical outcomes in patients with renal cell carcinoma treated with temsirolimus. Although these findings must be validated prospectively, it should also be determined if this marker is a true mechanism-based toxicity or an epiphenomenon associated with therapy. *Clin Cancer Res*; 18(11); 2999–3001. ©2012 AACR.

In this issue of *Clinical Cancer Research*, Lee and colleagues report, through a retrospective analysis, that increased levels of serum cholesterol are a potential predictor of clinical efficacy of temsirolimus in patients with advanced renal cell carcinoma (RCC; ref. 1).

Two rapalogues, temsirolimus and everolimus, are now approved by the U.S. Food and Drug Administration for the treatment of patients with advanced RCC. Treatment with rapalogues, allosteric inhibitors of the kinase mTOR, has been associated with several metabolic abnormalities, including hypercholesterolemia (2). The exact mechanism by which the rapalogues induce hypercholesterolemia is unknown. As Lee and colleagues discuss, the mTOR pathway has been implicated in the regulation of sterol regulatory element binding proteins (SREBP)-1 and SREBP-2, which in turn are master transcriptional regulators of fatty acid and cholesterol biosynthesis, respectively (Fig. 1). The authors propose that attenuation of SREBP activity may underlie the hypercholesterolemia associated with temsirolimus. However, it has recently been shown that many functions of SREBP-2, in particular the regulation of cholesterol biosynthesis genes, are dependent upon mTOR complex 1 (TORC1) but resistant to rapamycin (3). It is perhaps more likely that the recent finding that low density lipoprotein (LDL) receptor gene expression is dependent upon TORC1 and sensitive to rapamycin more directly contributes to rapalogue-induced hypercholesterolemia (4). Regardless, this toxicity seems characteristic of mTOR inhibitors, and its correlation to clinical outcomes has previously been unstudied.

In this issue, Lee and colleagues present the results of a retrospective analysis of the correlation between changes in fasting serum cholesterol, triglycerides, and glucose during treatment and clinical outcome measures in patients treated

with temsirolimus and IFN- $\alpha$  as part of the Global Advanced RCC Trial (1). In their analysis, the authors show that larger increases in serum cholesterol from baseline in patients treated with temsirolimus were associated with both reduced risk of disease progression and prolonged overall survival. Strikingly, when the effect of cholesterol change was accounted for through multivariate analysis, there was no additional advantage to temsirolimus over IFN. Moreover, both greater baseline serum cholesterol and larger increase in serum cholesterol during treatment were associated with improved clinical outcomes regardless of treatment arm. The authors, therefore, conclude that change in serum cholesterol may be a promising predictive biomarker of response to mTOR inhibitors.

Lee and colleagues stress that this retrospective analysis is meant to be hypothesis generating, and indeed, many questions come to mind. First, why is greater baseline serum cholesterol associated with better clinical outcomes regardless of treatment arm? This finding is curious, given that some studies have linked obesity and high-cholesterol diets with risk of RCC development (5, 6). RCCs have been shown to contain elevated levels of cholesterol esters (7), leading some to speculate that both the enzyme responsible for cholesterol ester formation, acyl-coenzyme-A:cholesterol acyl transferase (ACAT), and LDL-mediated uptake may be critical for RCC progression (8), implying that RCC with less LDL import may simply be less aggressive or metabolically active. It is also possible that baseline serum cholesterol may be more representative of nutritional status, perhaps even more relevant in the poor-risk population studied in the Global Advanced RCC Trial. In this light, baseline serum cholesterol may be more of a prognostic marker independent of treatment, rather than predictive. One might also speculate whether this marker would continue to be prognostic or predictive in patients who have favorable risk features.

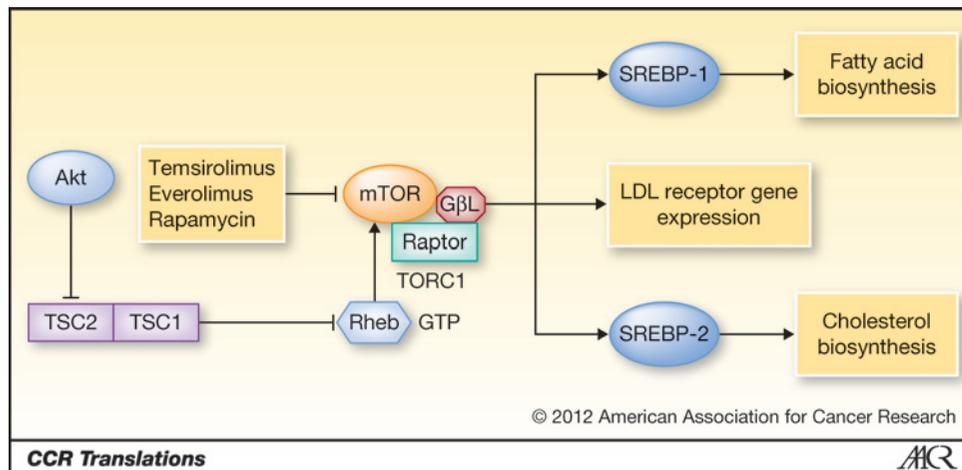
The most provocative finding of this analysis, however, remains that greater increase in serum cholesterol during treatment was associated with improved clinical outcomes across the study. Although the authors focus on the predictive value with respect to temsirolimus, the fact that this finding was independent of treatment arm raises an

**Authors' Affiliations:** <sup>1</sup>Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; <sup>2</sup>Georgetown Lombardi Comprehensive Cancer Center, Washington, District of Columbia

**Corresponding Author:** Daniel C. Cho, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, MASCO 4, Boston, MA 02215. Phone: 617-632-9250; Fax: 617-632-9260; E-mail: dcho1@bidmc.harvard.edu

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**Figure 1.** Regulation of fatty acid and cholesterol biosynthesis and LDL receptor gene expression by mTOR. Raptor, regulatory-associated protein of mTOR; RHEB, Ras homolog enriched in brain; TSC1, tuberous sclerosis complex 1; TSC2, tuberous sclerosis complex 2.

important question: Is the increase in serum cholesterol during treatment a true mechanism-based toxicity or an epiphenomenon? One might speculate that tumor cells that are proliferating less rapidly would require less lipid and cholesterol for generation of new cell membrane. Although it is likely that the majority of lipid and cholesterol required for cell membrane is generated through *de novo* biosynthesis, rapid proliferation may require enhanced cholesterol import. Therefore, increase in serum cholesterol might be an epiphenomenon indicative of slowed tumor growth, rather than a marker of the degree of mTOR inhibition.

On the other hand, the most current understanding of the biology of the mTOR pathway supports the belief that the observed increase in serum cholesterol may be a pharmacodynamic marker. In addition to the mechanistic rationale that rapalogues have been shown to induce changes in gene expression that would be expected to reduce cholesterol uptake, this belief is supported by the fact that, in the current analysis, serum cholesterol was not observed to change significantly in patients treated with IFN. The correlation of mechanism-based toxicities with improved clinical outcomes is a familiar paradigm with other molecularly targeted agents. Examples include skin rash with EGF-pathway inhibitors in patients with non-small cell lung cancer and hypertension with VEGF receptor-2 (VEGFR2) antagonists in patients with RCC (9, 10).

The distinction between epiphenomenon and true mechanism-based toxicity is critical, as with the latter, the failure to observe an increase in serum cholesterol would suggest inadequate suppression of the biologic target in normal tissue and could serve as a surrogate for the same in tumor cells. In this case, the dose of temsirolimus might be escalated until an increase in serum cholesterol is observed. This approach might be even more feasible with temsirolimus than with other molecularly targeted agents, as phase I trials identified a recommended phase II dose of up to 250 mg i.v. once weekly, significantly in excess of the standard 25 mg i.v. once weekly dose approved in RCC (11). On the other hand, in a large phase II trial in which patients with advanced RCC were randomized to receive temsirolimus at doses of 25 mg, 75 mg, and 250 mg i.v. once weekly, no

differences in efficacy were noted among the treatment arms (12). As inpatient dose escalation of temsirolimus has not been studied, however, further retrospective analysis to confirm a correlation between plasma concentrations of temsirolimus and serum cholesterol levels in these trials would be helpful in supporting the feasibility of and rationale for this concept.

In summary, the work presented by Lee and colleagues provides many avenues for future research. As with any retrospective analysis, these findings must be validated prospectively and independently. Should increase in serum cholesterol be validated as a predictive biomarker of temsirolimus efficacy, this measure could be used to more rapidly identify patients who would not be expected to benefit from treatment. Given the unique biology of RCC, it would be interesting to determine whether serum cholesterol is similarly predictive of benefit of mTOR inhibitors in different cancer types. If changes in serum cholesterol levels in RCC are more of an epiphenomenon associated with therapy, would this marker be similarly predictive of benefit with VEGFR inhibitors? Finally, perhaps the most enticing possibility is that increase in serum cholesterol may be a true mechanism-based toxicity that can be used as a pharmacodynamic surrogate. Should this prove to be the case, consideration might be given to the prospective study of inpatient dose escalation of mTOR inhibitors in patients with RCC.

#### Disclosure of Potential Conflicts of Interest

M.B. Atkins is a consultant to Novartis and received honoraria from Pfizer. No potential conflicts of interest were disclosed by the other author.

#### Authors' Contributions

**Conception and design:** D.C. Cho, M.B. Atkins

**Writing, review, and/or revision of the manuscript:** D.C. Cho, M.B. Atkins

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