Title: Sirolimus inhibits key events of restenosis in vitro/ex vivo: Evaluation of the clinical relevance of the data by SI/MPL- and SI/DES-ratio's

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Author's response to reviews: see over
Dear BMC editorial team,

enclosed please find revision II of our manuscript entitled: “Sirolimus inhibits key events of restenosis in vitro/ex vivo: evaluation of the clinical relevance of the data by SI/MPL- and SI/DES ratio’s”.

The authors would like to thank the referee for fair and constructive criticism. The queries of the referee have been carefully addressed, changes in the manuscript have been clearly marked.

We hope that the manuscript can now be accepted for publication in BMC-Cardiovascular Disorders.

With best wishes

Priv.-Doz. Dr. Rainer Voisard
Sirolimus inhibits key events of restenosis in vitro/ex vivo: evaluation of the clinical relevance of the data by SI/MPL- and SI/DES ratio’s

Reviewer I (Rober L. Wilensky):

Q1: I am still confused by the findings shown in Figure 1. I assume that the readership would be confused as well and so the authors should describe the findings in greater detail.

A1: Figure 1 was redone.

Q2: The authors bring up an excellent point on page 18 in which they indicate that determination of the SI/MPL-ratio may have allowed for better design of clinical studies. A couple of examples would greatly strengthen the manuscript.

A2: In background, page 4, paragraph 3, line 7, the following phrases were added: “Failed systemic restenosis trials in the 80ies and 90ies of the past century have caused an estimated loss of 2.5 billion € to the pharmaceutical industry (13,14), indicating the need for tools to predict the clinical relevance of positive in vitro data. Recently our group has suggested to apply a SI/MPL-ratio, characterizing the relation between a significant antiproliferative effect of a substance in vitro (SI) and the maximal plasma level (MPL) of this substance after systemic administration (13,14). A SI/MPL-ratio < 1 characterizes an agent that has at least a theoretical chance to achieve positive effects after systemic administration (e.g. positive antiproliferative effects) and after local high dose administration. If the SI/MPL-ratio is > 1, it describes how many times the positive in vitro concentration is above the MPL. In this case the agent has a mere local high dose option, e.g. in a drug eluting stent (DES).”

In discussion, page 18, paragraph 2, was rewritten: “Due to the fact that the application of the SI/MPL-ratio (13, 14) might have stopped many negative systemic restenosis trials in the 80ies and 90ies, saving an estimated loss of 2.5 billion € of the pharmaceutical industry (14), the usefulness of the SI/MPL-ratio is convincing. Due to antiproliferative SI/MPL-ratio’s > 1, prednisolone (SI/MPL-ratio: 7.1; 28), dexamethasone (SI/MPL-ratio: 6.6; 28), cyclosporine A (SI/MPL-ratio: 11.1; 29), iloprost (SI/MPL-ratio: 10; 30), triazolopyrimidine (SI/MPL-ratio: 4.86; 31), diltiazem (SI/MPL-ratio: 104.2; 32), and abciximab (SI/MPL-ratio: 11.4; 33) should not have been applied in clinical studies rationally based on a significant antiproliferative effect. Antiproliferative SI/MPL-ratio’s < 1 have been reported of the cytostatic agents cytarabine (SI/MPL-ratio: 0.1; 34), doxorubicine (SI/MPL-ratio: 0.83; 34), etoposide (SI/MPL-ratio: 0.0021; 34), paclitaxel (SI/MPL-ratio: 0.002; 30) and of the immunosuppressive agents hydrocortisone (SI/MPL-ratio: 0.043; 28), sirolimus (SI/MPL-ratio: 0.01; 13), and mycophenolate mofetil (SI/MPL-ratio: 0.0011; 13). These agents have at least a theoretical chance to reproduce an antiproliferative effect after systemic administration. The application of a SI/DES-ratio is suggested for the first time in the current study. Drug concentrations in current DES are extremely high (26), resulting in SI/DES ratio’s between $10^{-6}$ and $10^{-8}$. This is overdone and may partially cause the problems of late thrombosis in DES (35). Probably antiproliferative SI/DES-ratio’s between $10^{-1}$ to $10^{2}$ are sufficient to create a significant local antiproliferative effect. Drug concentrations in DES will be the central issue of the future. It has to be demonstrated, if the SI/DES-ratio can close a little bit the gap between bench and bedside by keeping the focus on the relation between effective drug concentrations in vitro and the local concentration in
DES.”

The corresponding references were added:


Q3: SI/MPL ratio should be defined in the introduction when it is initially introduced, not in methods.

A3: please see A2, part 1.

Q4: There are numerous syntax and grammatical errors. Also the term is dose dependent not dose dependency.

A4: Syntax and grammatical errors were removed.

Q5: The statement on page 15, 1st paragraph discussing the possible role of fibronectin and the
possibility that it is in the fetal calf serum is confusing and should be eliminated.

A5: Data on the effect of sirolimus on cell migration are very limited, therefore we had to refer on the work of Sakakibara et al. (18).