Format for ANSWERING REVIEWERS

January 23, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15311-Review.doc).

Title: Secondary amyloidosis in auto inflammatory diseases, the role of inflammation in renal damage

Author: Roberto Scarpioni, Marco Ricardi and Vittorio Albertazzi

Name of Journal: *World Journal of Nephrology*

ESPS Manuscript NO: 19484

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

（1）***Reviewed by 00503252***

a. Include the statement that chronic inflammation may contribute to progression of acute or chronic kidney disease in the Introduction section: **done**.

b. The author described that "A worse renal outcome in patients with chronic sepsis or Crohn's disease was reported, possibly related to the high frequency of surgical intervention and administration of immunosuppressive drugs, which probably contributed to renal failure in patients with Crohn's disease (P13, L5-8)." Please cite appropriate references and mention as to how the high frequency of surgical intervention and administration of immunosuppressive drugs could contribute to renal failure: **A worse renal outcome in patients with chronic sepsis or Crohn's disease was reported[28], possibly related to the high frequency of surgical intervention and administration of immunosuppressive drugs, probably due to greater severity of disease associated or not at increased risk of infection[personal unpublished data].**

c. Minor NALP3 (P1, L4 from the last line) ? AKI (P5, L14)? HD (P6, L1)? FCAS (P13, L9)? NOMID/CINCA(P13,L9)? TPX (P18,L13): **done**.

（2）***Reviewed by 00503339***

A clearly written and potentially important perspective on the pathogenesis of renal injury in Amyloidosis as well as other diseases that afflict similar metabolic paths. The impact of

this contribution might be increased by listing a series of Key Points made as well as a List of Potentially Helpful Clarifying Studies. Thank you for your suggestions. I agree that listing a series of key points might be helpful for a better comprehension of the links, but unfortunately, the close concatenation of the arguments, in my opinion, do not permit it.
On the other hand, Main Manuscripts potentially helpful Clarifying:

- Mulay SR, Kulkarni OP, Rupanagudi KV, Migliorini A, Darisipudi MN, Vilaysane A, Muruve D, Shi Y, Munro F, Liapis H, Anders HJ. Calcium oxalate crystals induce renal inflammation by NLRP3-mediated IL-1β secretion. *J Clin Invest* 2013; 123: 236–246. doi: 10.1172/JCI63679. Epub 2012 Dec 10. PMID: 23221343 [PubMed - indexed for MEDLINE] PMCID: PMC3533282
- Lichtnekert J, Kulkarnit OP, Mulay SR, Rupanagudi KV, Ryu M, Allam R, Vielhauer V, Muruve D, Lindenmeyer MT, Cohen CD, Anders HJ. Anti-GBM glomerulonephritis involves IL-1 but is independent of NLRP3/ASC inflammasome-mediated activation of caspase-1. *PLoS One* 2011; 6: e26778 doi: 10.1371/journal.pone.0026778. Epub 2011 Oct 27. PMID: 22046355 [PubMed - indexed for MEDLINE] PMCID: PMC3203143
- Scarpioni R, Rigante D, Cantarini L, Ricardi M, Albertazzi V, Melfa L, Lazzaro A. Renal involvement in secondary amyloidosis of Muckle-Wells syndrome: marked improvement of renal function and reduction of proteinuria after therapy with human anti-interleukin-1β monoclonal antibody canakinumab. Clin Rheumatol 2015 Jul;34(7):1311-6. [Epub ahead of print] doi: 10.1007/s10067-013-2481-2. Epub 2014 Feb 9. PMID: 24510061 [PubMed - in process]
- Anders HJ, Muruve DA. The inflammasomes in kidney disease. J Am Soc Nephrol 2011; 22(6):1007-18. doi: 10.1681/ASN.2010080798. Epub 2011 May 12.
- Turner MC, Arulkumaran N, Singer M, Unwin RJ, Tam FWK. Is the inflammasome a potential therapeutic target in renal disease? *BMC Nephrology* 2014; 15:21. doi: 10.1186/1471-2369-15-21
- Merlini G, Bellotti V. Molecular Mechanisms of Amyloidosis. *N Engl J Med* 2003; 349:583-596 DOI: 10.1056/NEJMra023144 PMID: 12904524

One caution to be considered (and mentioned) is the often noted finding that results based on Intermediary Metabolism in rodents may not be extended to humans:–I Agree. "The administration of anti-human SAP antibodies[47] to mice with amyloid deposits containing human SAP triggers a potent, complement-dependent, reaction that swiftly removes massive visceral amyloid deposits without adverse effects. These promising results achieved in mouse models based on intermediary metabolism may not be extended to humans, so specific trials are needed to test this hypothesis also in humans.

（3）***Reviewed by 00503187***

a. Suggestions: Please write out AA in the title: **done**.

b.Also throught the text, please write out the shortenings the first time they appear (HD, RCT): **I agree, it was done.**-Please check for grammatical errors and typos and that the language is English (autoinflammatory is one word; modified from..; LEGEND and not LEGENDA. ROS does not appear in Table 1 and is mentioned.. **done**

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Nephrology*

Sincerely yours,

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