"Answering Reviewer"

No	Reviewer	"**Response**" (See the **manuscript** pl):
(1)	**03475636** **Anonymous** **2017-09-27 02:11**	**VIII: *De novo* IgAN**: IgAN has been one of the most common GN worldwide. Graft loss has been frequently reported with *recurrent* IgAN [8]. On the other hand, this fate is rarely reported with *de novo* IgAN [111]. ***Incidence***: *De novo* IgAN has been reported to be less common than recurrent IgAN [112]. Considering the high frequency of asymptomatic IgAN, some authors argue that *de novo* IgAN might be considered as "transmitted disease", which means that recipient received an allograft that already had a "latent" form of IgAN [14], this argument is supported by the finding that a considerable percentage of mesangial IgA deposition (16.1 %) has been reported in 0-hour protocol biopsy performed by a Japanese study [113]. ***Histopathology***: Intracapillary proliferation with a possibility of crescent formation can be observed in many biopsies. IgA and C3 granular deposits in the glomerular capillary wall and mesangium are frequently seen in IF studies. ***Clinical features***: despite the presence of frequent IgA deposition, *de novo* IgA is frequently asymptomatic especially in Asian population that may be discovered only in protocol biopsy. *Course and prognosis*: in case of presence of crescent formation in allograft biopsy, prognosis of *de novo* IgA is ultimately poor, otherwise course and prognosis is quiescent with mild mesangial hypercellularity [8]. For example, Robles et al, (1991) reported a case of de novo IgAN with progressive proteinuria, microscopic hematuria and rapid deterioration of allograft function after renal transplantation in a patient with ESRD due to MPGN [4]. On the other hand, *De novo* Henoch-Schönlein purpura has been described post renal transplantation with a rapid graft loss [114, 115]. **VIII: Treatment of de novo IgA:** For mild and moderate *de novo* IgA, no specific therapy is advised. However, Shabaka et al (2017) reported that potentiation of immunosuppressive therapy with CNI and augmentation of RAS blockade can lead to a complete remission and better renal function [111]. On the other hand, Carneiro-Roza (2006) and his colleagues reported a better initial response in decreasing urinary protein level with no improvement in renal function [146]. In patients presented with crescentic IgAN and a rapidly progressive course, pulse steroid, cyclophosphamide and PE may be tried with expected poor results [14]. ***Retransplantation***: No contraindication to retransplant (table 4). ***Anti-VEGF therapy related de novo PLA2R-negative membranous nephropathy***: The role of vascular endothelial growth factor (VEGF) in angiogenesis is well documented [42, 43]. Local (intravitreal) and systemic (IV) anti-VEGF therapy have been recently introduced in many diseases. Systemic (IV) therapy has been used in the management of advanced cancer therapy. Unfortunately, this type of therapy has been associated with several untoward effects e.g. hypertension, hemorrhage, proteinuria and thromboembolic events [44]. On the other hands, local (intravitreal) route is usually well tolerated [45], due to its low administrated dose and the localized nature of injection. However, clearance of these agents has individual variations that may be reflected as systemic insults [46]. Recently, Wisit Ch and his colleagues (2015) reported two cases of allograft dysfunction that are related to the administration of intravitreal anti-VEGF therapy [46]. First case developed MN with spherular deposits after one year of initiation of therapy [47]. Moreover, PLA2R antibodies were reported to be negative in biopsy and no anti-PLA2R antibodies were detected in serum [48, 49], which favours the de novo

		nature of MN, as only one third of idiopathic MN can express the lack of anti-PLA2R antibodies [48, 49]. The increased level of proteinuria was not due to MN, as no evidence of immune complex GN in subsequent biopsy (4 months), which is in agreement with other reports [49, 50]. The second case has long standing decline but stable renal function, it showed progressing proteinuria observed few months after initiation of therapy with a clear evidence of both acute and chronic AMR in allograft biopsy [51]. ***Relation to proteinuria***: appearance of proteinuria in anti-VEGF treated patients is reported to be related to the start of anti-VEGF therapy, a finding that is supported by allograft biopsy findings (microspheruler substructure variant of MN) properly due to a new antibody formation or unmasking of already present anti-HLA antibodies. The appearance of proteinuria is clearly related to the systemic use of anti-VEGF in cancer patients [44]. An observation that can be explained by the well documented effect of VEGF on preserving the glomerular filtration barrier integrity [42, 52]. Moreover, an altered VEGF activity has been proposed to be a potential aetiology of mTOR inhibitors-induced proteinuria [53]. On the other hand local (intravitreal) administration of anti-VEGF may lack this effect [45]. A given explanation may be due to its different formulation and the local route of administration. However, clearance of these agents is ultimately systemic [45]. Furthermore, a recent report recorded a precipitous decline of allograft function (GFR <25 mL/min per 1.73 m2) in a group of anti-VEGF treated patients [54]. ***Mechanism of renal injury***: the following mechanisms have been postulated as a given explanations for allograft injury: (1) Disruption of the normal survival signals mediated by VEGF leading to creation of alloreactive antibodies or exaggerated renal allograft injury induced by the already present antibodies. (2) Loss of the mitigating effect exerted by VEGF on CyA toxicity [55]. (3) Unmasking action on the already present anti-HLA antibodies. (4) Renal allograft susceptibility to anti-VEGF-induced injury leading to an increased tissue marker expression, including HLA and non-HLA antibodies. (5) Evolution of Antibody-mediated rejection through anti-HLA antibodies production [46]. The exact role of anti-VEGF agents' interference in allograft biology is complex, necessitating more extensive investigations [56-58]. ***Recommendations***: Two recommendations have been proposed in the context of anti-vascular endothelial growth factor (VEGF) therapy: **Firstly**: RTR should be strictly monitored through at least monthly determination of urinary proteins. **Secondly**: The threshold index for allograft biopsy should be lowered, with application of both IF and EM studies [46].
(2)	**00504406** **C Fourtounas** **2017-10-07 18:55**	EXCELLENT REVIEW WITH SIGNIFICANT EDUCATIONAL VALUE FOR EVERYBODY INVOLVED IN RENAL TRANSPLANTATION ….. (**No suggestions**).
(3)	**00503243** **Maurizio Salvadori** **2017-09-20 12:27**	**VIII**: ***De novo* IgAN:** IgAN has been one of the most common GN worldwide. Graft loss has been frequently reported with *recurrent* IgAN [8]. On the other hand, this fate is rarely reported with *de novo* IgAN [111]. ***Incidence***: *De novo* IgAN has been reported to be less common than recurrent IgAN [112]. Considering the high frequency of asymptomatic IgAN, some authors argue that *de novo* IgAN

might be considered as “transmitted disease”, which means that recipient received an allograft that already had a “latent” form of IgAN [14], this argument is supported by the finding that a considerable percentage of mesangial IgA deposition (16.1 %) has been reported in 0-hour protocol biopsy performed by a Japanese study [113].

Histopathology: Intracapillary proliferation with a possibility of crescent formation can be observed in many biopsies. IgA and C3 granular deposits in the glomerular capillary wall and mesangium are frequently seen in IF studies.
Clinical features: despite the presence of frequent IgA deposition, *de novo* IgA is frequently asymptomatic especially in Asian population that may be discovered only in protocol biopsy.
Course and prognosis: in case of presence of crescent formation in allograft biopsy, prognosis of *de novo* IgA is ultimately poor, otherwise course and prognosis is quiescent with mild mesangial hypercellularity [8]. For example, Robles et al, (1991) reported a case of de novo IgAN with progressive proteinuria, microscopic hematuria and rapid deterioration of allograft function after renal transplantation in a patient with ESRD due to MPGN [4]. On the other hand, *De novo* Henoch-Schönlein purpura has been described post renal transplantation with a rapid graft loss [114, 115].

VIII: Treatment of de novo IgA:

For mild and moderate *de novo* IgA, no specific therapy is advised. However, Shabaka et al (2017) reported that potentiation of immunosuppressive therapy with CNI and augmentation of RAS blockade can lead to a complete remission and better renal function [111]. On the other hand, Carneiro-Roza (2006) and his colleagues reported a better initial response in decreasing urinary protein level with no improvement in renal function [146]. In patients presented with crescentic IgAN and a rapidly progressive course, pulse steroid, cyclophosphamide and PE may be tried with expected poor results [14].

Retransplantation: No contraindication to retransplant (table 4).

- For editors revision, ALL the requirements are fulfilled.
- Thanks and best regards.