Grenda R, J Nephrol Renal Ther 2017, 3: 012
DOI: 10.24966/NRT-7313/100012

HSOA Journal of Nephrology & Renal Therapy

Editorial

Biologics in Nephrotic Syndrome

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Nephrotic syndrome is a complex disease related to variety of underlying mechanisms. The minority of cases are related to podocyte microstructure abnormalities developing due to the specific genetic mutations, which from clinical point are associated with primary resistance to steroids and immunosuppression [1]. The non-genetic forms are regarded as the effect of different "protein permeability factors", the heterogenous family of cytokines which bind specific targets on podocytes, impact their functionality and shape and provoke/maintain the clinically overt proteinuria. These include the permability factor primarily described by Savin et al. [2], Cardiothropin-like Cytokine-1 (CLC-1) [3], soluble urokinase-Type Plasminogen Activator Receptor (suPAR) [4] and anti-CD_{40} antibody [5]. The podocytes by themselves may also generate dysfunction of it's local metabolism, which provokes negative cross-talk with other tissues, which release cytokines promoting podocyte injury, such as angiopoietin-like-4 factor [6,7]. The classic view on therapy of nephrotic syndrome was focused on effect of steroids and immunusoppressive drugs on specific immune cells, mainly lymphocytes T and B. The current view on this therapy points also the potential of local, podocytes-targeting mechanisms of some biologic drugs, including rituximab and abatacept. Rituximab, depleting monoclonal antibody anti - B CD_{20} was used in third-line therapy of steroid (or immunosuppression)-dependent nephrotic syndrome, both in primary disease and in recurrence after renal transplantation [8-11], mainly basing on B-cell related mechanism. Some reports were optimistic, some other-more reluctant. There are data, suggesting that rituximab may exert specific local mechanism on podocyte, which is indepedent from it's effect on B CD_{20} receptor, and is related to stabilisation of podocyte's cytoskeleton via regulation (preservation) of Sphingomyelin Phosphodiesterase Acid-Like 3b (SMLPD-3b), a protein which is involved in the podocyte cytoskeleton activity [12,13]. This may lead to speculations, that only partial remission seen in some treated patients or the lack of correlation between number of peripheral CD_{20} cells (or CD_{19}; used for monitoring of the drug effect) and clinical efficacy (seen also in some patients) are the result of local, not systemic mechanism of rituximab. Is the dosing regimen used for systemic action (4 x 375 mg/m2 of BSA) adequate also for local effect-is not clear.

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Citation: Grenda R (2017) Biologics in Nephrotic Syndrome. J Nephrol Renal Ther 3: 012.

Received: January 04, 2017; **Accepted:** January 06, 2017; **Published:** January 20, 2017

CD_{80} (B7-1) is a molecule present on the surface of T cells, dendritic cells and podocytes. So called "two-hits hypothesis" claims, that immune response to the external trigger (e.g., viral infection) in fully immunocompetent humans is limited to transient expression of CD_{80} on podocytes, which (not necessarily) may cause short-term proteinuria. Humans with specific predisposition, like sustained dysregulation of regulatory T cells (T_{regs}) react to the similar trigger with sustained expression of CD_{80} in podocytes, which via dysregulation of cytoskeleton, leads to long lasting proteinuria (nephrotic syndrome) [14]. High urine excretion of CD_{80} is being regarded as biomarker of minimal change disease [15]. CTLA-4 (Cytotoxic-T-Lymphocyte-Associated Protein-4), present on podocytes and T_{regs} is important co-factor in this mechanism [16] . Blocking of CTLA-4 with abatacept (CTLA-4-Ig) may ameliorate proteinuria. Primary report was optimistic, showing the efficacy of abatacept in 4 (of 5) cases, resistant to other drugs, including rituximab [17]. Further reports were more reluctant and did not confirm preliminary therapeutic enthusiasm [18,19]. Probably, the use abatacept should be limited to the cases, in whom the renal biopsy (native or transplant) confirms the local expression of B7-1 (CD_{80}) in podocytes or at least urinary excretion of CD_{80} is markedly increased. These cases remind us, that increasing availability of modern biologic drugs, with high affinity to specific receptors, not necessarily provide universal therapeutic success in clinical practice. Mundel and Greka have recently published in article, claiming availability of the "therapeutic arrows with the precision of William Tell" in kidney diseases [20], however clinicians must not forget that pre-emptive finding of the right shooting target is indispensable part of further therapeutic success.

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