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# Targeted complement inhibition as a promising strategy for preventing inflammatory complications in hemodialysis

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## Hemodialysis.com Authors' Interview:



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*Hemodialysis.com* Editor Marie Benz: What are the main findings of the study?

**Our review was influenced by our recent study published in *Blood* (vol. 116: 631-9) demonstrating that biomaterials used in hemodialysis in patients with end-stage renal disease (ESRD), especially the polysulfone fibers used in many hemodialysis filters, are capable of inducing activation of the complement cascade and generation of the anaphylatoxin C5a, which can promote tissue factor production and procoagulant activity by polymorphonuclear cells (neutrophils) in the blood.**

**Importantly, treatment with compstatin, a small peptide inhibitor of complement that acts upstream of C5a generation, was able to prevent or significantly reduce the activation of neutrophils, their production of tissue factor, and their procoagulant activity normally induced by blood circulation through an extracorporeal circuit (similar to that used in hemodialysis).**

**Compstatin treatment also reduced the production of the pro-inflammatory cytokines IFN- $\gamma$ , IL-1RA and G-CSF by neutrophils.**

**These results suggest that inhibiting complement activation can reduce the tissue factor-dependent procoagulant activity of polymorphonuclear cells during hemodialysis, as well as the production of pro-inflammatory cytokines, which can contribute to thrombosis and other complications.**

***Hemodialysis.com*: Were any of the findings unexpected?**

**In experiments in which neutrophils were incubated with blood from healthy donors or ESRD patients, the addition of polysulfone fibers reduced modified prothrombin time (mPT), which is inversely correlated to procoagulant activity. This indicated that the fibers induced an increase in neutrophil procoagulant activity (regardless of the presence of disease).**

**Amazingly, pre-treatment with compstatin was able to increase mPT back to approximately 90% of the levels seen when no fibers were added, suggesting that compstatin could almost completely block the effects of the fibers. Additionally, in our extracorporeal circulation model, compstatin wholly prevented**

**complement activation in the blood and severely reduced the production of tissue factor by neutrophils, again showing a potent ability to block procoagulant activity.**

**Though we expected inhibition of complement to positively affect these parameters, the strength of the effect was somewhat surprising.**

***Hemodialysis.com:* What should clinicians and patients take away from your report?**

**One of the important points of our work is the demonstration of a potential therapeutic option for hemodialysis patients to limit thrombosis and related complications through the use of compstatin, which is already in clinical trials for the treatment of age-related macular degeneration, and has so far shown no adverse side effects.**

**Due to the cheaper costs of production for small peptide drugs, compstatin has the potential to become a cost-effective treatment for patients on hemodialysis to improve their overall quality of life.**

***Hemodialysis.com:* What recommendations do you have for future research as a result of this study?**

**One important point that we demonstrated was that polysulfone filters (all hemodialysis patients in the study used these filters) and fibers (in our *in vitro* assays) could induce complement activation and TF-dependent procoagulant activity in neutrophils. Though this is a popular material for hemodialysis filters, other polymers are used, and it would be interesting to see if our findings could be applied to these materials, as well. This would also determine how universal the potential for therapeutic treatment with compstatin would be.**

**Importantly, results from these studies could be applied not only to hemodialysis but also other situations in which biomaterials come into contact with tissues.**

**Additionally, we found an increase of several inflammatory cytokine in our extracorporeal circulation model, including IFN- $\gamma$ , IL-1RA (both of which were inhibited by compstatin), and IL-17, which have either not yet been strongly linked to hemodialysis and/or coagulation, or which have an unclear role in these conditions.**

**Thus, further research is needed to determine the significance of these findings. Finally, our results concerning the inhibitory effects of compstatin, as well as a tested C5a receptor antagonist, may contribute to future therapeutic studies for both soluble inhibitors and the coating of biomaterials with inhibitory compounds to**

**prevent complement activation and related adverse situations, and these avenues should be further pursued.**

**Reference:**

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