

Clinical Trials For Dense Deposit Disease

Wellcome Trust Conference Centre, Hinxton, Cambridge UK

Conference: Third International Focus Group Meeting on Dense Deposit Disease, August 15-17, 2008

Participants: Thirty-three delegates from 11 different countries attended this conference, which was divided into six interactive sessions.

Report: The first interactive session focused on the epidemiology and pathology of Dense Deposit Disease (DDD). Epidemiological data were presented to show that DDD is more aggressive in younger patients. Rate of progression to endstage renal failure (ESRF) is higher in this age group; young girls appear to be more likely to progress to ESRF. Dr. Patrick Walker reported on the histologic spectrum of DDD and described four different subtypes of disease: mesangial cell hypercellularity (45%), membranoproliferative (25%), crescentic (18%) and acute proliferative and exudated (12%). There appears to be no correlation between outcome and light microscopic appearance although numbers are small.

Dr. Sanjeev Sethi then presented laser capture-mass spectroscopy (LC-MS) data to define the proteins in DDD glomeruli. In addition to identifying components of the alternative pathway (AP) of complement, components of the terminal complement complex (TCC) were also present. ApoE was uniquely present in DDD as compared to normal and immune complex-mediated

membranoproliferative glomerulonephritis (IC-MPGN). Factor H-related proteins (FHRP) were identified by LC-MS in glomeruli from both DDD and IC-MPGN.

Interactive Session II focused on the response of the kidney to the dense deposits. Dr. Van Der Vlag presented data showing that heparanase is up regulated in DDD and heparan sulfate proteoglycans are destroyed. Dr. Quaggin presented data on podocyte damage in DDD. It is not clear whether this damage is primary or secondary to the deposits that develop in the GBM. Dr. Alexander presented data showing that DDD is reversible if glomerular crescentic changes have not developed.

The third interactive session focused on the role of complement. Dr. Zipfel focused on the importance of dysregulation of the AP in the pathogenesis of DDD. He also discussed the significance of FHRP-1, which is found in DDD glomeruli, but also in glomeruli from IC-MPGN. The significance of this finding is unclear. Whether the presence of FHRP-1 is protective or an epiphenomenon is unknown.

Interactive Session IV focused on the genetics of DDD. Dr. Smith presented data showing a composite at-risk genotype based on risk alleles in five different genes. These data clearly show that DDD is a complex genetic disease that requires an environmental trigger. The role of Factor H was reviewed by Dr. Hageman in the context of age-related macular degeneration (AMD). The significance of the H402 polymorphism and its relationship to the development of drusen was considered. Dr. Hageman presented preliminary data on patients undergoing liver transplants with the resultant change in their genotype from the

at-risk Factor H allele to the protective Factor H allele. He reported that in some of these patients, AMD resolves.

Interactive Session V focused on therapeutic options in DDD. Discussion focused on recombinant Factor H, Compstatin, a C3 antibody to scavenge C3 breakdown products, fusion proteins and heparanase inhibitors. Dr. Levidiotis commented on the last option, recognizing that the Phase 2 trial in the United States looking at Sulodexide in the treatment of diabetes was unsuccessful. She felt that this result maybe relate to drug manufacture techniques. Dr. Smith discussed two fusion proteins designed to scavenge C3 breakdown products including iC3b, C3c an C3dg. Preliminary data show that one of these fusion proteins decreases activity of the AP *in vitro* as assayed by the degree of MAC activation. *In vivo* experiments are ongoing using these agents in mouse mutants homozygous for the targeted deletion of Factor H.

The final interactive session focused on clinical trials in DDD. Dr. Norris discussed trial design and monitoring efficacy, calling attention to the similarity between DDD and Fabry's disease. She also noted that DDD has a protracted natural history, which can make studies on treatment logistically difficult to perform. Additional difficulties include power calculations, interim analyses, recruitment, and choice of primary and secondary efficacy endpoints given the limited number of affected patients. Enrollment in Europe and North America were compared. Dr Salant concluded by reviewing the possibility of global enrollment.

Conclusion: The meeting realized its specific goals by clarifying the pathogenesis of DDD, identifying several compounds that warrant close consideration as possible therapies for DDD, and discussing trial design.