IDIOPATHIC MEMBRANOUS NEPHROPATHY

Post-Bergamo- 2011

Summation Remarks at the 2nd International Conference on Membranous Nephropathy

Bergamo, IT

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May 8, 2011
When this Conference was conceived more than 2 years ago, the Planning Committee did not fully appreciate its impeccable timing. The field of Membranous Nephropathy (MN) is now in the early stages of what Thomas Kuhn called a “paradigm shift”. After many years of relative stasis where the rate of acquisition of new information was about equal to the rate that older information was being discarded, so that the total informational content was in equilibrium. As a result of several major “breakthroughs” (detailed below), we now find the field in a state of disequilibrium where the accelerated rate of new information generation greatly exceeds the discard rate of older information and the total informational content of the field has expanded markedly. This meeting incorporated this salutary state of affairs and like the best of scientific meetings raised at least as many question as those that were answered by the presentations and discussion, both formal and informal.

The Planning Committee* is deeply grateful to the sponsors, The Halpin Foundation, Amgen France, Genentech, Genzyme and QuestCor for their support without which this meeting would not have been possible. We are also grateful to the many investigators who agreed to come to Bergamo and share their exciting new data. The participation of patients with MN added a much appreciated dimension to the meeting. The tireless effort of Ariela Benigni, Giuseppe Remuzzi and C.E.C Servizi Staff were key factors in the success of the meeting.

Membranous Nephropathy - A new naming opportunity and our indebtedness to Walter Heymann

Were it not for the quirk of fate that the silver methenamine stain and electron microscopy were applied to examination of MN before studies of the immunoglobulin composition of the deposits in the “idiopathic” disorder were described, it is possible that the name for what we now call MN could have been “IgG4 dominant nephropathy”, as the role of autoantibodies of the IgG4 subclass in the pathogenesis MN is now reasonably well established, and made firmer by the results presented at this meeting. In addition, we must acknowledge the very important role for the pioneering studies of Walter Heymann and his followers in defining the experimental model of membranous nephropathy in the rat studies of this model and all of its variations, still ongoing, have made critical contributions to our understanding of the human disease.
Membranous nephropathy - a podocytopathy of well defined pathogenesis -

Idiopathic Membranous Nephropathy (MN) is now regarded as a proto-typical immune-mediated podocytopathy defined by its characteristic morphology. MN is a disorder that commonly results in Nephrotic Syndrome in Adults but uncommonly so in Children. The etiology of MN is mostly unknown in Adults but is commonly due to infections, diet (cows milk consumption), or systemic auto-immune disease in Children. Auto-immunity underlies the pathogenesis of the great majority (75-80%) of apparently Idiopathic MN in Adults, most commonly involving and IgG4 dominant auto-antibody to podocyte-specific PLA2R, forming immune complexes in-situ. (Idiopathic MN may be a part of the family of IgG4 related diseases). Other antigen-antibody systems may participate in Idiopathic MN (BSA, SOD2, AR, NEP, CCT, enolase, etc).

Both in-situ and planted antigen mechanisms can result in similar (if not identical) patterns of injury. The mechanisms underlying the formation of visible deposits and their growth and persistence in the sub-epithelial space remains uncertain. The interaction of these deposits with GBM (e.g. Type IV Collagen chains) requires further study. The mechanisms underlying the formation of visible deposits (by the electron microscope or by special stains by light microscopy) and their growth, attachment to the underlying glomerular basement membrane (GBM) and persistence in the sub-epithelial space remains uncertain. The interaction of these deposits with GBM (e.g. Type IV Collagen chains) requires further study.

The trigger(s) for auto-antibody production (to conformational epitopes on PLA2R) are largely unknown, but may involve processes of molecular mimicry, enhancement of natural immunity or activation of an auto-reactive T-cell repertoire. We know the identity of the target(s), the bullet(s), the gun but not the shooter in IMN.

Idiopathic Membranous nephropathy – susceptibility –

Susceptibility to Idiopathic MN is associated with to HLA-DQ gene loci (Chromosome 6) and to specific PLA2R SNPs (intronic) (Chromosome 2) as a “digenic” phenomenon, perhaps influencing protein folding and antigen presentation (PURE SPECULATION). The specific locations of immuno-dominant epitope(s) on the exo-domains of PLA2R are not yet known with certainty (but soon will be).
**Idiopathic membranous nephropathy - the podocyte**

Engagement of anti-PLA2R auto-antibody with the PLA2R auto-antigen on the podocyte surface may evoke a stereotypical “stress-like” reaction of podocytes leading to activation of both injurious and protective cellular pathways, the balance of which determines the outcome for podocyte dysfunction and survival (manifested as albuminuria and glomerular sclerosis). Local Complement activation (MBL and alternative pathway) and its regulation, intracellular enzyme pathways, apoptosis regulating factors, T-cell (CD8) derived soluble factors undoubtedly play roles in podocyte dysfunction and proteinuria.

**Idiopathic membranous nephropathy – prognosis**

Idiopathic MN is endowed with a *self-limited* natural history. The factors involved in spontaneous resolution, relapses, persistence or progression are largely unknown. Accurate prediction of natural history and response to intervention (s) at the time of recognition of disease is under-developed at present, but promising avenues are emerging (e.g. urinary Beta 2 microglobulin assays). This deficiency (hopefully a temporary one) inhibits application of “personalized medicine” approaches to individual. Refinement of *serum, tissue and/or urinary biomarkers* show great promise in individualized prognostication and determination of therapeutic responsiveness in Idiopathic MN (See Table 1).

**Table 1 - BIOMARKERS**

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<tr>
<th>Serum Auto-antibodies</th>
<th>immuno-phenotyping</th>
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<td>Tissue Transcriptomics</td>
<td>patho-typing</td>
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<tr>
<td>Urinary Proteomics</td>
<td>bio-typing</td>
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A Broad Consensus exists that a *remission* (CR or PR) of nephrotic-range proteinuria represents one of the best and most readily available *surrogate* biomarkers of outcome in Idiopathic MN. The utility of repeated measures of additional urinary biomarkers (e.g. NGAL, KIM-1, UIgG,
UBeta2M, etc.) for provision of prognostic information is extremely promising but further validation in larger cohorts followed for longer periods of time is desirable (a multiple biomarker panel may be required for optimal discrimination). However, the evidence that measurement of urinary biomarkers represents a substantial improvement over simple assessment of quantitative proteinuria and its change over time in terms of long term prognosis remains inconclusive.

**Idiopathic Membranous nephropathy – treatment**

As was made very clear at the meeting, we have a number of effective treatments for IMN- we just don’t know how to apply them in a maximally efficient and cost-effective fashion in individual patients. Any of the agents listed in Table 2 have been shown to be effective in IMN although the strenght of the evidence varies from agent to agent.

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<th>Table 2 - THERAPIES FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY</th>
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<td><strong>Alkylating Agents</strong></td>
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<tr>
<td><strong>Calcineurin Inhibitors</strong></td>
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<tr>
<td><strong>Rituximab</strong></td>
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<td><strong>ACTH</strong></td>
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<td><strong>MMF</strong></td>
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At the present time there are no validated or reliable biomarkers for prediction of responsiveness (or probability of a spontaneous remission) to specific therapies in Idiopathic MN. Failure to respond to one treatment regimen does not reliably predict responsiveness to further treatment with another regimen in a different therapeutic class. Complement inhibition or regulation (Systemic [Eculizumab] or Site Directed [CR-2 Fusion Protein]) might be the next generation of therapies for Idiopathic MN. In addition, anti-oxidants and chelator of free iron and ACTH may have important new effects on MN - worthy of further study and exploration.

Therapeutic interventions in Idiopathic MN may be acting systemically (on B or T-cell subsets, chemokines, cytokines or growth factors) or locally (on podocyte function/survival, C-activation
inhibition). Resolution of mechanism(s) of action of therapeutic agents may help to design safer and more effective dosing, sequencing or combination drug strategies.

*Idiopathic membranous nephropathy – Areas of uncertainty in BASIC SCIENCE –*

- What are the specific gene-environment interactions that “trigger” Idiopathic MN?
- What processes underlie the growth, persistence and resolution of sub-epithelial immune deposits?
- Why is Idiopathic MN an IgG4 associated disease? What is the role of IgG1 in Idiopathic MN?
- What is the nature of the immuno-dominant epitope(s) on PLA2R?
- Does intra- and/or inter-molecular epitope spreading play a role in determining the character of Idiopathic MN in humans?
- How long before clinical onset of disease can auto-antibodies be detected?
- What injurious and protective mechanisms are engaged at the podocyte level in Idiopathic MN? Can they be modified?
- Are IMN-associated PLA2R and HLA-DQ SNPs identified by GWAS the causal pathway for disease development?

*Idiopathic membranous nephropathy - Areas of uncertainty in CLINICAL SCIENCE –*

- How will measurement of anti-PLA2R auto-antibody transform the clinical approach to diagnosis and management (remission induction and relapse free maintenance therapy) of Idiopathic MN?
- How will serum, tissue and/or urine biomarkers be used to refine prognostication and therapeutic decision-making? (“personalized medicine”)
- Can new rationally-designed therapeutic strategies acting at the podocyte level be developed and tested in man (e.g. Complement modulation; podocyte survival promoters, anti-oxidants, enzyme/cytokine inhibitors, etc)?
- Can currently available drugs be applied in a more effective manner (dosing, sequencing, combinations)?
Can systematic examination of recurrent MN in renal allografts shed light on the factors responsible for the nascent origins of MN?

Whatever the future brings the Bergamo Membranous Nephropathy meeting will long be remembered for its place in the history of this intriguing disorder.
* Planning Committee for the 2nd International Conference on Membranous Nephropathy

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