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New Aspects on Pathogenesis and Treatment of Membranous Glomerulopathy

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Abstract

The membranous nephropathy (MN) is the major cause of nephrotic syndrome in the adult, account for 20% of cases with annual incidence of 1/100.000.

In the past 10 years the role of podocytes has been identified; environmental triggers in genetically predisposed patients can activate podocytes to exhibit antigenic epitopes (receptor of phospholipase A2, thrombospondin type 1) that become targets of specific auto antibodies with subsequent complement activation. The discovery of these mechanisms has opened new horizon in the therapy of MN and novel drugs are available with more specific mechanism of action.

Rituximab, a monoclonal antibody directed against CD20 expressed on lymphocytes B, has been used in several trials and appears able to induce remission of nephrotic syndrome in 60% of patients (GEMRITUX trial) with similar risk profile. Nowadays it remains to define the most effective therapeutic pattern. In MN, the concept of targeting disease control has permit novel therapies with specific blocking mechanisms (belimumab) and non-specific (ACTH) and new therapeutic options, such as ofatumumab, bortezomib and eculizumab, that have allowed recognizing pathological processes involved in the glomerular diseases.

Keywords: *Podocyte, Membranous glomerulonephritis, membranous nephropathy, Rituximab, Eculizumab, New trials*

Introduction

Membranous nephropathy (MN) is the most frequent cause of nephrotic syndrome in adults and old patients. It accounts for 20% of nephrotic syndromes in adults and its annual incidence is 1/100000 inhabitants. Overall in Europe 10000 new cases per year are diagnosed (1).

In the last 10 years the pathogenetic mechanisms have been defined and this fact opened new ways of treatment.

Research Methodology

Because aim of this review is to find out what is really new in pathogenesis and treatment of MN, we have analyzed the available papers on MN pathogenesis and MN therapy by a review of the currently available papers. A literature search was performed using PubMed (NCBI/NIH) with the search words "MN pathogenesis", "MN therapy". As first line research the papers published in the last three years were examined. Paper selection has been made according the relevance of the journal, the authors, the dimension of the study and the novelty of the findings. So doing 20 papers recently published have been selected, then we proceeded in a backward way and studies previously published have also been included. Studies currently under way were searched for in "clinical trial.gov". As clinical trial.gov also includes studies to date that are either closed or have not started, we selected only randomized controlled trials (RCTs) that are active and enrolling patients.

Etiology and Pathogenesis

In the last years MN has been found to be essentially a disease of the podocyte which, as a response to environmental triggers and on a genetic basis, exhibits antigen epitopes, which binds antibodies able to bind complement.

The first antigen to be recognized has been the neutral endopeptidase (NEP) by the team of Ronco (2). Later, a different protein of podocyte, the receptor of phospholipase A2 type M (PLA2R) has been found to be the antigen responsible for 70-80% of MN (3). As PLA2R is a normal molecule of the podocyte structure, MN may be regarded as an autoimmune disease at least in patients where antibodies anti PLA2R may be found (4). The discovery of the M type phospholipase A2 receptor (PLA2R) as a major antigen in idiopathic MN was a breakthrough in understanding the pathogenesis of this disease, establishing iMN as an autoimmune disease. Subsequent studies confirmed that detection of circulating antibodies against PLA2R was positive in approximately 70% of incident iMN patients. Recently, it has been shown that the presence of PLA2R antibodies supported a diagnosis of iMN, changes in antibody levels were related to clinical disease activity, disappearance of antibodies preceded and predicted subsequent decrease of proteinuria and high titers of antibodies were associated with a low likelihood spontaneous remission (5). Recently another antigen of podocyte, the thrombospondine type 1 domain containing 7A (THSD7A) has been found responsible of around 10% of MN (6).

Additionally the antigens of aldose reductase and superoxido dismutase have been suggested in some cases of MN (7).

As a consequence of these findings, for a better understanding of the disease and of possible new therapies, we are now looking for new markers of podocyte, able to activate the complement cascade and for cells able to produce the antibodies involved (8, 9).

The Toronto Registry of Glomerulonephritis found the Toronto Risk Score according which patients may be divided in low risk for progression, intermediate risk and high risk according the proteinuria levels in the first six months (10).

The team of Wetsels found markers predictive of evolution towards renal failure in alpha1 macroglobulin and beta 2 microglobulin excretion (11, 12).

The best marker of the disease evolution and the answer to treatment is the titer of anti PLA2R (13-15).

Treatment

The therapeutical options may be divided into 3 main categories.

a) The supportive treatment

b) The immunosuppressive therapy

c) The ongoing trials

Supportive Treatment

In a first period of the disease supportive treatment without use of immunosuppressants is recommended by KDIGO guidelines for all patients with MN and nephrotic syndrome (16).

It consists in restricting dietary sodium intake to less than 2g/die and controlling blood pressure, hyperlipidemia and edema.

In all patients angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) should be the first line therapy because of their antiproteinuric effect (17).

If patients remain with nephrotic syndrome or have nephrotic syndrome recurrence in the first six months of treatment, the immunosuppressive treatment should be considered.

Immunosuppressive Treatment

The combination of corticosteroids and cyclophosphamide or chlorambucil given over 6 months is best known as Ponticelli's treatment. Several studies documented a remission rate of 70-80% (18-20). Cyclophosphamide and chlorambucil are equally effective in inducing remission, but some study (21) has documented a better tolerability profile for cyclophosphamide. A prophylactic treatment with trimetoprim sulfametoxazole is recommended to avoid Pneumocystis pneumonia (22).

Anticalcineurine Drugs

Prospective, randomized studies documented the efficacy of cyclosporine A (CyA) and Tacrolimus (TAC) in the treatment of MN (23-25).

In addition to the immunosuppressive effect, CyA and TAC have an antiproteinuric effect due to their action on podocyte structure via interaction with sinaptopodin (26).

Main drawbacks of CyA and TAC are their nephrotoxicity and the high rate of recurrence when the drugs are reduced (27).

Mycophenolate Mofetil

Several, observational studies suggest the efficacy of mycophenolate mofetil in the treatment of MN (28).

However the only published controlled study did not document such efficacy (29). For these reasons, although the combination of MMF with a high dose of corticosteroids appears effective, the KDIGO guidelines do not recommend MMF as the first line of treatment for patients with MN (16).

Rituximab

Rituximab (RTX) is a monoclonal antibody directed against CD20 on the surface of B lymphocytes. In the case of MN, RTX is used with the aim to block the production of antibodies directed against the antigens aforementioned which characterize the MN.

Several patients treated by RTX in previous observational studies (30-33) documented the efficacy of RTX in MN with complete or partial remission of the nephrotic syndrome in 60% of patients. No treatment-related serious adverse events were reported in either study. The RTX doses in the different studies have principally been 375 mg/m^2/week for 4 weeks or 1 or 2 doses of 1g.

More recently, a controlled, prospective, randomized trial comparing two doses of 375 mg/m^2 with supportive treatment versus supportive treatment alone in 75 patients with MN was started. This is the GEMRITUX trial (34). The study results at 17 months documented a remission rate for RTX patients of 65 vs 34% ($p<0.03$).

Open question is which is the best therapeutic and regimen strategy with RTX and its efficacy on recurrence (35).

On these bases several ongoing trials attempt to compare RTX with cyclophosphamide or anticalcineurinic drugs using different RTX doses.

Ongoing Trials with Rituximab

4 randomized controlled trials with RTX are ongoing.

1) The Membranous Nephropathy Trial Of Rituximab (MENTOR) study (NCT01180036). This is an open label randomized controlled trial (RCT) designed to evaluate RTX (1 g iv day 1 and day 15, repeated after 6 months) versus CyA (3.5-5 mg/kg/day) for 6 months (36)

2) The Sequential treatment with Tacrolimus-Rituximab vs steroids plus cyclophosphamide in patients with idiopathic Membranous Nephropathy (STARMEN) trial (NCT01955187) will compare a TAC-RXT treatment with the Ponticelli's treated groups. Rates of remission, relapse, preservation of renal function will be evaluated in a 2-year follow up (37).

3) The NCT00977977 trial, which compare RTX and CyA. The CyA group will withdraw CyA after 6 months and introduce RTX.

4) The RI-CYCLO trial (NCT03018535) is recruiting MN patients in Italy to compare the efficacy of RTX with Ponticelli's schedule.

Acth

ACTH stimulates the production of endogenous glucocorticoids and activates the melacortin receptors, which play several functions among which immunomodulation, anti-inflammation and modulation of exocrine functions (38).

In rodents these receptors have been found in podocytes, glomerular endothelial cells, mesangial and tubular epithelial cells. In animal models affected by iMN, the inhibition of melanocortin receptors reduces proteinuria and improves podocyte morphology (39).

After a first pilot study (40), two studies (41,42) demonstrated the beneficial effects of natural ACTH in resistant glomerular diseases. Hladunewich et al (43) in a prospective open label study confirmed such beneficial results in 20 patients affected by iMN.

To date two studies still ongoing are registered in Clinical Trials.gov (NCT00694863 and NCT03025828).

New Experiences

Ofatumumab

Ofatumumab is new monoclonal antibody acting on CD20. It differs from RTX in term of different target epitopes. Indeed, ofatumumab in addition to act on the same epitope recognized by RTX, acts also on a second epitope localized on the small loop of CD20 and on a portion of the large extracellular loop (figure 1). Of atumumab has been assessed as RTX rescue therapy.

Ruggenenti et al. (35) recently described two cases of clinical remission of iMN in patients who developed primary and secondary resistance to RTX. Resistance to RTX could be due in these cases to a change in the CD20 antigen conformation, which prevents B cell-RTX binding and the consequent B-cell depletion.

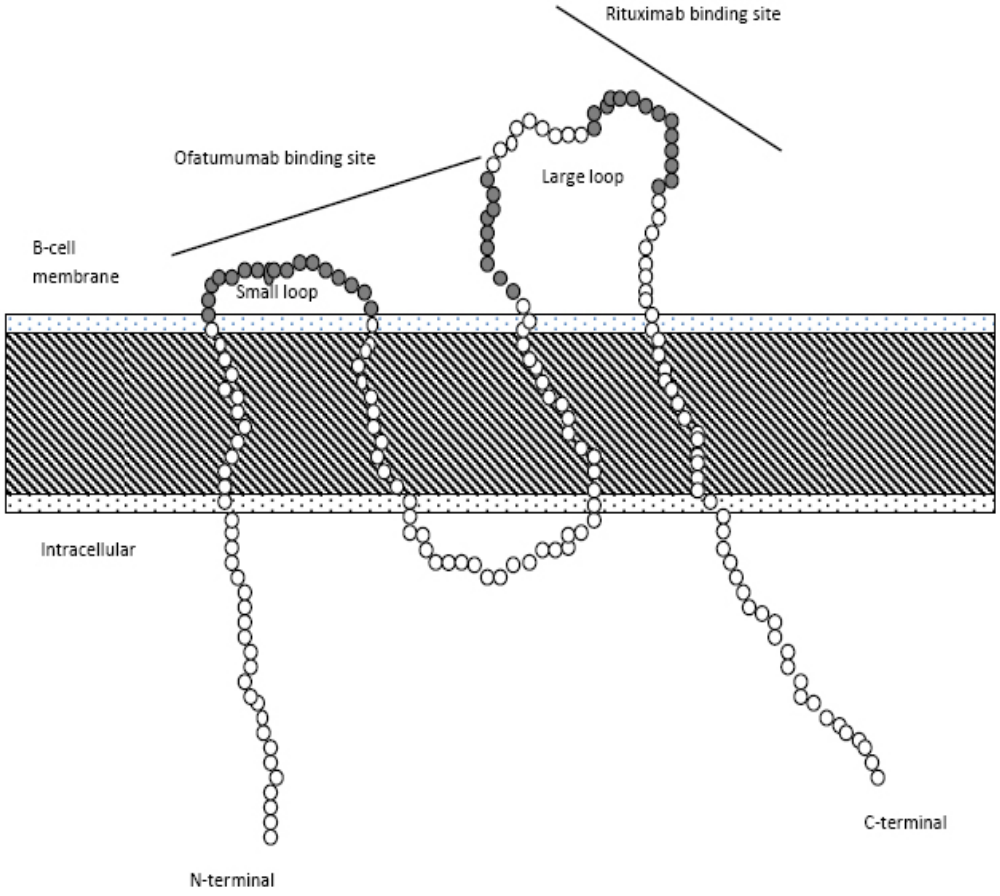

Fig 1. *The molecular configuration of the CD20 molecule*

Belimumab

A monoclonal antibody, belimumab, specifically targets the soluble form of B lymphocyte stimulator (BLyS) that has a critical role in the differentiation and homeostasis of B lymphocytes. The effects of belimumab on proteinuria and anti-PLA2R antibody production have been evaluated in 14 patients with anti-PLA2R positive MN. The treatment significantly reduced the antibody titer and proteinuria within 12 weeks (44). Changes in proteinuria and in anti-PLA2R antibody titer after belimumab treatment seemed to parallel the changes observed after RTX with a delay in onset. This may reflect the immediate B-cell lysis achieved by RTX, whereas the slower effect of belimumab might reflect the progressive "exhaustion" of antibody producing B cells secondary to BLyS binding and inhibition.

Targeting Memory Plasma Cells

According several authors, the advanced stages of MN could be mediated primarily by auto reactive plasma cells, which are resistant to anti-CD20 monoclonal antibodies but sensitive to anti-CD38 antibodies or proteasome inhibitors.

Memory plasma cells survive RTX because they do not express the CD20 antigen. Plasma cells express CD38 (45,46). These auto reactive plasma cells could be a target for anti-CD38 monoclonal antibodies, such as dataturumab and isatuximib. To date these agents have been developed to kill malignant plasma cells (46). Other molecules as proteasome inhibitor bortezomib may effectively deplete plasma cells. Bortezomib acts causing an intracellular accumulation of abnormal proteins with consequent plasma cell apoptosis.

To date bortezomib has been used in ANCA nephritis (47) and in resistant systemic lupus erithematosus (48). Preliminary data suggest its use in iMN resistant to other therapies (49,50).

Main drawback of bortezomib is its toxicity, which necessitate treatment interruption in most patients.

Targeting Complement

Complement inhibition by the anti C5 monoclonal antibody, eculizumab, could be another way for treating iMN. This is a fascinating approach because complement inhibition could prevent glomerular damage waiting for antibodies removal (51).

Unfortunately the only RCT did not document any antiproteinuric effect. Underdosing of eculizumab in the study could explain the ineffective complement inhibition (52).

Conclusion

The discovery of anti PLA2R antibodies and the other antibodies involved in the pathogenesis of MN has revolutionized our approach to this disease and for the first time we may consider MN as an autoimmune disease in which the podocyte play the initial and most important role. The possibility to monitoring the anti-PLA2R antibodies represents an important tool for the nephrologist to monitor the disease and to check the therapeutical effects.

RTX represents today the most important drug in the treatment of MN. Several relevant questions remains to be answered. Which is the most appropriate dosage? Which the role of the other immunosuppressants? What to do with the relapse? Several ongoing RCT try to answer these questions. Additionally the pipeline is fill with other new drugs which are all the subject of RCT.

Ofatumumab in the cases of MN resistant to RTX, drugs targeting the memory plasma cells and drugs affecting the complement pathway seem to be the most important for the future.

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