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When and how to treat patients with membranous glomerulonephritis?

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The management of idiopathic membranous glomerulonephritis (MGN) requires a global strategy that should necessarily be based on the differentiation of its several presenting forms. This statement, which should be applied to all glomerular diseases, is particularly important in MGN since its natural history without immunosuppressive therapy widely varies from one patient to another. It is therefore necessary to carefully analyse the data available in the literature about the natural history of this disease before discussing the different therapeutic options. We insist in this concept because therapeutic regimens based on the scheme «all or nothing» are still being published, which are absolutely far away from an individualized analysis of each patient. So, «nihilist» attitudes have been proposed not treating MGN patients with immunosuppressants due to the high percentage of a benign course.[1] By contrast, other authorities in the field sustain radically opposite positions, advocating managing all MGN with nephrotic syndrome with steroids and cytostatic agents.[2] We believe that the most correct attitude is in-between both extreme positions; we will try to sustain this idea in this article. We will describe the current policy on the management of MGN at the Nephrology Department of the 12 de Octubre Hospital. Obviously, the opinions and recommendations here expressed should be interpreted as a summary of our global policy based on an important cumulated experience, with different historical phases, and with retrospective and prospective studies gathered from several publications. However, we should not forget the scant number of controlled prospective studies on the management of MGN, making of the recommendations here expressed a matter of debate and opinion.

NATURAL HISTORY OF MGN

A differentiating feature of MGN is that a high percentage of cases present complete or partial spontaneous remission of the nephrotic syndrome in the absence of steroidal or other immunosuppressive therapy. The series of patients published during the 1970s and 1980s are very illustrative of this fact, since most of the patients with idiopathic MGN demonstrated by renal biopsy did not receive specific therapies. Based on these and some other more recently published series (revised in 3), the spontaneous remission rate could be of around 30%-45% of the cases.

By contrast, another considerable percentage of cases (of around 30%-35%)[3] develop progressive renal failure, ending-up in chronic dialysis when the process cannot reverted with drugs, as it will be commented further on. Within this unfavourable course, two different progression forms should be distinguished: a variable percentage of cases, of around 20%, develop rapidly progressing renal failure within few months, which sometimes is already present at the time of diagnosis. These cases, which we should call «aggressive MGN» or «rapidly progressing MGN», are always accompanied by massive proteinuria together with rapid renal function deterioration.[4,5] In another varying percentage of cases (15%-25%), renal failure development is slower, after a prolonged period (years) of nephrotic proteinuria.

This dichotomous evolution[4] is very characteristic of MGN and presents a number of particularities of great clinical importance that should always be taken into account when designing the global therapeutic regimen for this entity:

- Both benign (spontaneous remission) and aggressive forms are early defined in most of the patients: usually the first 12-24 months from the start of the disease are the period during which we will see either spontaneous remission or renal function deterioration. There are cases showing their progression later, although their likelihood decreases with time.
- The development of renal failure is constantly associated to the presence of massive proteinuria. In all the cases with partial remission (defined as proteinuria > 0.3-0.5 but not within the nephrotic range of 3.5 g/24 h) the long-term outcome is good.[6] Even in those cases with sustained nephrotic proteinuria < 4-5 g/24 h not accompanied by important hypoalbuminemia it is uncommon to observe rapid renal function deteriorations although the long-term likelihood of slowly-progressing renal failure increases with time.

From what have been said, and simplifying the different evolving variants of non-treated MGN, we may distinguish three main groups: 1) benign MGN characterized by the ap-

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pearance of complete or partial spontaneous remissions; 2) aggressive or «rapidly progressing» MGN, characterized by the development of rapid renal failure (within few months), accompanied by massive nephrotic syndrome; and 3) persistent MGN that maintains nephrotic syndrome for long periods without observing renal function deterioration or spontaneous remission. Although it is a simplification, each one of this variant would approximately represent one third of the patients with MGN. Of course, the therapeutic approach should be different in the differently evolving forms.

SPONTANEOUS REMISSIONS IN MGN

As previously mentioned, 30%-45% of the cases (with large differences between the different series) have spontaneous remission, i.e., without the use of steroids or immunosuppressants. A must corollary of this fact should be the implementation of an observation period in every patient with MGN, provided that his/her renal function does not show evident deterioration attributable to other functional factors. During this observation period, the general measures of nephrotic syndrome management have to be applied: relative rest, a salt-free diet, diuretics according to the patient's progression, management of hyperlipidemia with statins, and prescription of ACEIs or angiotensin receptor antagonists (ARA) to achieve BP values < 130/80 mmHg and profit from their anti-proteinuric action. The consequences of hypercoagulability in patients with nephrotic syndrome must be prevented (risk for deep venous thrombosis/pulmonary embolism) by using low-molecular weight heparins in those patients with anasarca or confined to bed.

Several works, especially those from Cattran's group, have shown that male gender, age older than 50 years, and the presence of sustained proteinuria > 8 g/day for longer than 6 months are criteria for a poor prognosis, and thus lower likelihood of spontaneous remission.[7] It is likely, however, that the incidence of spontaneous remissions in MGN has increased in recent years, maybe in relation with the generalized use of ACEIs and/or ARA and statins from diagnosis. In a preliminary analysis from our group (data not published), we have observed that the incidence of spontaneous remission was significantly higher among patients early treated with ACEIs/ARA, and that even patients meeting the above-mentioned criteria for a poor prognosis could have spontaneous remissions in the absence of immunosuppressive therapies.

The duration of the observation period with conservative management is difficult to define given the lack of specific studies on this field, although from the clinical experience of our group we have established it around 12 months.[8] However, an important flexibility is necessary with these limits because in those cases with a clear trend towards decrease in proteinuria, although still being within the nephrotic range, it is convenient to extend this period beyond the first year in order to observe whether the patient enters or not in partial remission without aggressive therapy. Of course, by increasing the observation period the likelihood of spontaneous remission increases (although less and less common as time goes by), as well as that of specific complications from nephrotic syndrome and renal function deterioration. For this reason, in those cases with sustained massive proteinuria, not showing a decreasing trend and with bad tolerance to the nephrotic syndrome, it may be reasonable to shorten the observation period to 6-9 months[3] and decide on specific therapeutic measures, that we will discuss later on.

AGGRESSIVE FORMS OF MGN

Those cases initiating a rapid deterioration of renal function, almost always associated with massive proteinuria, should be excluded from the previous concept of conservative observation. Similarly to what happens with spontaneous remissions, it is within the first 12-24 months from diagnosis when these aggressive forms present. Before establishing this diagnosis, it is necessary to rule out that renal function deterioration is due to other functional factors (abuse of diuretics, collateral effect of ACEIs/ARA, etc.). Although there are no controlled prospective studies specifically aimed at these patients, we do have available studies on historical cohorts showing a very poor prognosis in those cases not receiving immunosuppressive therapies, as compared with treated ones.[9,10] In our experience,[9] virtually all the historical non-treated cases progressed to end-stage RF or died, whereas in treated cases the renal survival rate at 8 years reached 90%.

What kind of immunosuppressive therapy is preferred in these aggressive forms? The most popular immunosuppressive regimen for MGN is, with no doubt, that from Ponticelli's group, based on high-dose steroids (odd months) alternating with chlorambucil (even months), for 6 months.[2] We have used a regimen similar to Ponticelli's, although simplified by administering steroids exclusively p.o. (prednisone 1 mg/kg/day) with progressive reduction of the chlorambucil dose during 6 months, (0.15 mg/kg/day) for the first 14 weeks.[9] Other authors prefer steroids plus cyclophosphamide, administered for a longer time,[10] taking into account that cyclophosphamide has shown better efficacy and safety profiles than chlorambucil in a controlled study.[11]

In a prospective controlled study, anti-calcineurin agents (cyclosporin) have shown a favourable effect in MGN cases with renal function deterioration.[12] However, in our experience, managing anti-calcineurin agents in renal failure patients, especially if rapidly progressing, is particularly difficult so that, in the absence of comparative controlled studies, we prefer the classical immunosuppressive regimens (steroids plus chlorambucil or cyclophosphamide) in these presentation forms.

The concept being advocated[9,10] of «specific or restrained» immunosuppression, i.e., limited to those patients with rapid renal function deterioration, certainly is a matter of debate since it confronts with the proposal (mainly advocated by Ponticelli) of using immunosuppressive therapy in all the cases with nephrotic syndrome, without an observation period as we propose. However, we believe it necessary to undersco-

re that these therapeutic approaches are accompanied by frequent and serious adverse events,[9] so that it seems logical to limit their use to those cases with poorer evolution. On the other hand, Nijmegen's group from Holland, which defends an position similar to ours,[10] has shown in a careful analysis that a restrictive use of immunosuppressive regimens does not decrease their effectiveness while renders many patients spontaneously evolving towards remission free from the side effects of these drugs.[10]

FORMS WITH PERSISTENT NEPHROTIC SYNDROME

As previously stated, approximately one third of the MGN cases will show persistent nephrotic syndrome for years, without spontaneous remission or renal function deterioration.

As with all the therapeutic aspects of MGN, there also exists controversy in such cases. A purely conservative attitude could be advocated taking into account the possibility of late spontaneous remissions, although, as mentioned earlier, such probability decreases with time. By contrast, the structural damage caused by sustained nephrotic proteinuria has clearly been endorsed in recent years by experimental models and clinical studies.[13]

The studies by Ponticelli, using his regimen of steroids plus chlorambucil or cyclophosphamide, still are an obliged reference since they showed in a prospective and controlled way the efficacy in treated patients as compared to not treated ones.[2,11] Recently, another randomised prospective study with a long follow-up period showed that therapy with steroids plus cyclophosphamide was superior to no-treatment in MGN.[14] As mentioned, however, the main defect of these works is that they include all patients with nephrotic syndrome without a cautious observation period and without the generalized use of ACEIs or ARA, which seems to be a must in every patient with proteinuric glomerulopathy such as MGN.

The other therapeutic alternative that has consolidated over the last years in patients with nephrotic syndrome and sustained renal function is anti-calcineurin agents. In a multicenter controlled study, it was shown that the patients treated with steroids and cyclosporin for 6 months presented higher remission rates (68% *versus* 22%) than those only treated with steroids. One year after treatment discontinuation, the difference was reduced (43% *vs* 19%) due to frequent relapses when discontinuing cyclosporin, although it still was significant.[15]

In a recently published multicenter Spanish study,[16] it was shown that monotherapy with tacrolimus, at relatively low doses (initial dose of 0.05 mg/kg/day), achieved a rate of partial or complete remissions significantly higher than that in the non-treated group: 58%, 82%, and 94% at 6, 12, and 18 months of therapy in the treated group *versus* 10%, 24%, and 35% in the control group. An important finding was that the number of patients withdrawn from the study due to renal function deterioration was significantly lower in the treated group (just one patient versus 6 in the control group). The side effects from tacrolimus were few, without differences with the control group. However, after tacrolimus discontinuation, nephrotic syndrome recurred in 47% of the patients having achieved remission while taking the drug. Important novelties from this study were tacrolimus administration without accompanying steroids, the requirement of an observation period in all patients to assure persistence of the nephrotic syndrome, and the administration of ACEIs or ARA in all patients from both groups before and during the treatment period.

To find out what type of immunosuppressive therapy (steroids + cytostatic agent or anti-calcineurin agents) is more effective in these cases of MGN, a prospective controlled study would be required. However, there are comparison pilot studies showing a better profile with anti-calcineurin agents: higher remission rates, more rapid occurrence of remissions, and less side effects in the short and long terms.[17,18].

Given the cumulated experience and the good results obtained, at our centre we treat this type of patients with persistent nephrotic syndrome with tacrolimus. However, the main problem is relapse after drug discontinuation, which occurs in approximately half of the patients within the following months. This experience is similar to that obtained in Cattran's study with cyclosporin[15] and that from other recently published studies that have confirmed the effectiveness of tacrolimus, but also accompanied by frequent relapses upon treatment discontinuation.[19] The re-administration of anti-calcineurin agents is generally followed by a new remission, existing thus «anti-calcineurin-dependent» patients with the subsequent risk for nephrotoxicity in the long run.

A therapeutic alternative allowing discontinuation of the anti-calcineurin agent once the remission has been achieved and without relapse of the nephrotic syndrome would be paramount for managing this disease.

FORMS WITH CHRONIC RENAL FAILURE OR WITH INTOLERANCE OR A LACK OF RESPONSE TO ANTI-CALCINEURIN AND CYTOSTATIC AGENTS

It is not exceptional to detect patients with established CRF due to late diagnoses, previous inappropriate management, or patient's withdrawal from routine controls, which are paramount in this disease. On the other hand, the treatments referred so far, essentially steroids + cytostatic or anti-calcineurin agents are not always effective, and sometimes are not tolerated by the patient. A recently published multicenter study done in our country[20] has shown in these cases the efficacy of mycofenolate administered as «salvage therapy» for several glomerular diseases: in the cases with MGN (n = 21), after 12 months of therapy, proteinuria was reduced from 7.9 ± 2.1 to 3 ± 1.4 g/24 h and 52% of the cases entered partial remission with renal function stabilization.

OTHER THERAPEUTIC OPTIONS

In the last years, preliminary works have described the possibility of using rituximab and ACTH injections in MGN.[21,22] We believe that, although being very interesting, these op-

tions have to be corroborated by means of prospective controlled studies. It is convenient to underline that isolated administration of steroids, without cytostatic or anti-calcineurin agents, has not shown a beneficial effect in prospective controlled studies.[23]

SUMMARY AND RECOMMENDATIONS

In the algorithm shown in Figure 1 we summarize the current policy for MGN management followed at our Department, based on the arguments previously discussed. We believe that a general conservative therapy for nephrotic syndrome should be prescribed in every patient with MGN, including ACEIs or ARA and statins, and wait for a reasonable time period (about 12 months) to see whether or not spontaneous remission (complete or partial) occurs. In those cases with massive proteinuria not showing a decreasing trend, and especially in male patients aged > 50 years, it is reasonable to shorten the observation period. In aggressive cases, with massive proteinuria and starting with progressive renal function deterioration not attributable to other functional factors, our policy is based on the administration of a course of steroids plus chlorambucil, although the courses with steroids + cyclophosphamide seem to be equally effective and may be better tolerated. In those cases with persistent nephrotic syndrome and normal renal function that is sustained beyond the reasonable observation period, we start on tacrolimus monotherapy, maintained for approximately 12 months, thereafter initiating a progressive reduction for another 6 months. In those cases with nephrotic syndrome relapse after tacrolimus discontinuation, we re-administer the drug at the least effective dose to maintain the patient at least in partial remission. Finally, in those cases refractory to the measures stated, or that do not tolerate the drug regimens, we consider a course of mycofenolate for one year, with a slow dose reduction for the following 6-12 months in case of response. In those patients with established chronic renal failure (late diagnosis, loss to follow-up) and evident signs of chronicity, as well as in those (infrequent)

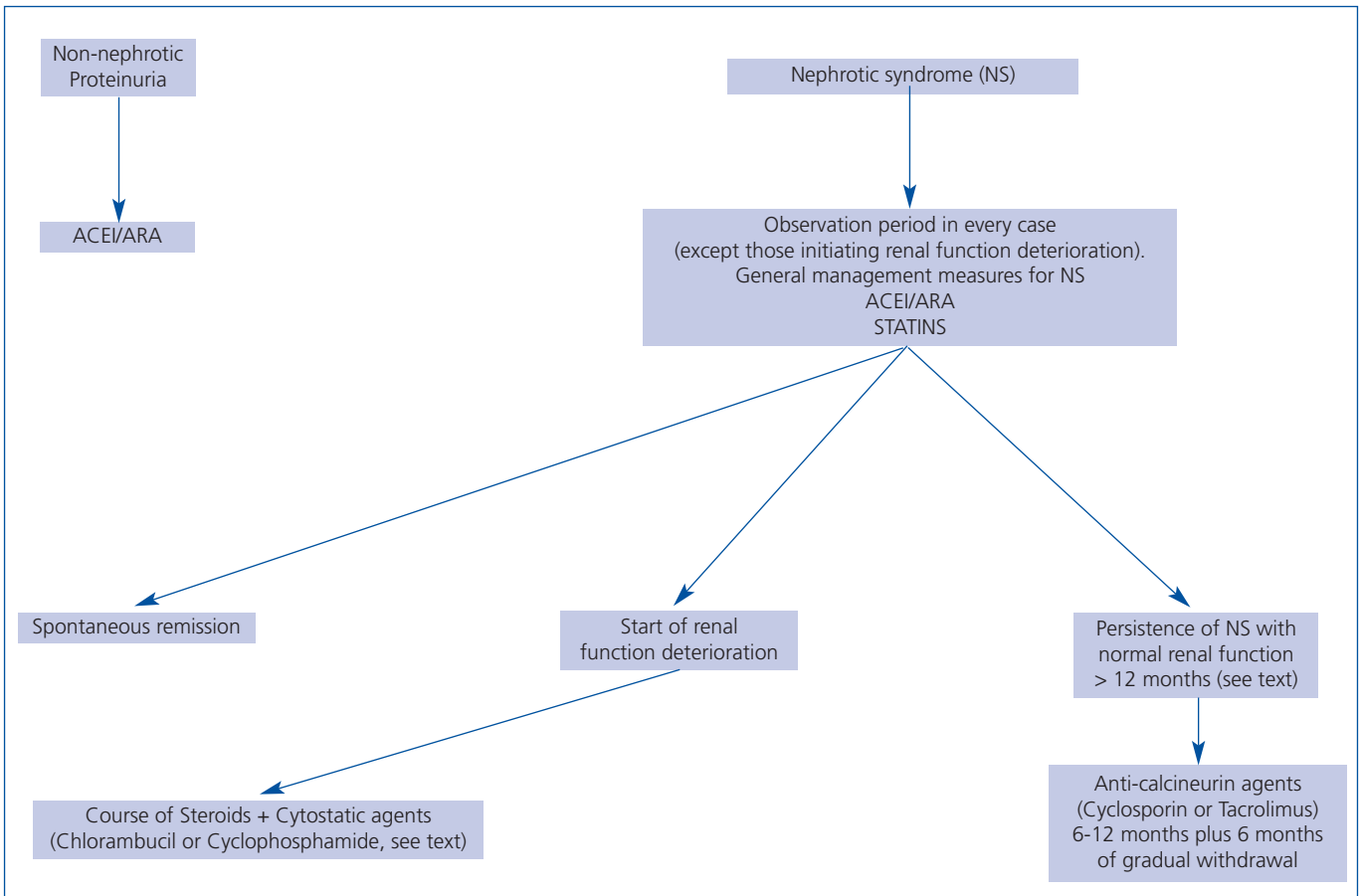

Figure 1. Therapeutic scheme of idiopathic MGN.

cases with non-nephrotic proteinuria we only prescribe general conservative therapy. The optimisation of renin-angiotensin system block with ACEIs, ARA, or combined ACEIs/ARA therapy, seeking the least amount of proteinuria possible is essential is the latter cases, as well as in those having developed partial remissions, either spontaneous or induced by immunosuppressive therapy.

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