Treatment of $\beta_2$-microglobulin amyloidosis by extracorporeal therapies other than haemodialysis, by medication and by surgery

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Introduction

The clinical management of $\beta_2$-microglobulin ($\beta_2$-M)-associated amyloidosis remains a difficult task. A causal treatment is not known at present, and arrest of the disease and full prevention probably can be obtained only by successful renal transplantation [1].

Since this type of amyloidosis has never been observed in the absence of markedly elevated plasma $\beta_2$-M, it has been deduced that the predialysis plasma $\beta_2$-M concentration should be kept as low as possible. The use of highly permeable, synthetic dialysis membranes, such as AN69 polyacrylonitrile and polysulfone F60, lowers its concentration significantly [2-6]. With haemofiltration and haemodiafiltration, even lower pretreatment plasma $\beta_2$-M can be achieved than with high performance haemodialysis techniques (Fig. 1a). Unfortunately, even with these techniques plasma $\beta_2$-M values remain much above the normal range.

Extracorporeal adsorption of $\beta_2$-M via haemoperfusion

Recently, new methods have been proposed for the treatment of dialysis-related amyloidosis, based on the principle of extracorporeal adsorption of $\beta_2$-M to adsorption columns. Two groups of Japanese workers evaluated the efficacy of columns composed of porous cellulose beads containing a hydrophobic hexadecyl-alkyl-adsorbing compound [7,8]. The haemoperfusion columns were connected in series to the arterial line of a high performance haemodialyser, constructed with either PMMA or AN69 PAN membrane. Both groups treated small numbers of haemodialysis patients thrice weekly for short periods of time (from 1 week to 1 month). In two patients in one group and three patients in the other, the treatment procedure was maintained for 6 months or more. The authors achieved an acute reduction of plasma $\beta_2$-M of 65% or more during the treatment session, which however is no better than the reduction achieved with high performance haemofiltration (Figure 1b). The long-term tolerance appeared to be excellent. It was unclear from the published data whether predialysis plasma $\beta_2$-M had decreased or not. Any statistical evaluation of data was impossible due to the small numbers of individuals studied.

Recently, a similar approach has been evaluated by two European groups of workers who tested the capacity of novel affinity adsorbents to remove $\beta_2$-M from aqueous solution. However, experience with these new methods has remained limited to in vitro studies. The first group [9] examined various affinity ligands, including alkyl residues with various chain lengths, collagen, and gelatin carriers. The latter two exhibited good adsorption performances. The second group [10] developed immunoadsorption columns, using murine monoclonal antibodies directed against human $\beta_2$-M. They optimized the procedure by varying the antibody density and flow rate of the antigen-containing solution. However, the problem of the stability of the immunoaffinity supports has not yet been entirely solved, so that antibodies could be released from carrier material. The latter two approaches must be considered as highly preliminary since no clinical experience is as yet available.

Importance of predialysis plasma $\beta_2$-M

It must be pointed out that no convincing evidence has ever been provided for the contention that the lower the predialysis plasma $\beta_2$-M concentration, the lower might be the prevalence of dialysis-associated amyloidosis. In fact, no relation was found between the circulating concentrations of the protein and the frequency of this complication, based on clinical evidence [11].

Dialysis techniques and end-points of clinical relevance

From a clinical point of view, it is important to define dialysis treatment strategies that could arrest or prevent $\beta_2$-M amyloidosis. The problem is that at present no
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Easily accessible, quantitative assessment of the disease process is at hand. Histological proof, which is reliable in terms of diagnosis, requires an invasive procedure. However, it does not allow evaluation of the extension and the activity of the disease process, except in post-mortem studies. We have recently proposed to use a mathematical model based on the plasma kinetics of i.v. administered radiolabelled P component for this purpose [12]. We still need to validate our approach in a prospective study comparing different treatment strategies. Another promising method is the recently developed scintigraphy with ¹¹¹In-labelled β₂-M which not only reduces radiation exposure markedly, compared with ¹³¹I-labelled β₂-M, but also provides an improvement in optical resolution [13]. However, its usefulness for quantitative disease assessment has still to be seen. Moreover, the problem of demonstrating the inocuity of a protein of human origin used for the injection into patients has to be solved. For the time being, one has to rely on established clinical and radiological features of β₂-M amyloidosis.

A lower prevalence of clinical and radiological manifestations of β₂-M amyloidosis, such as carpal tunnel syndrome [14] and characteristic bone cysts adjacent to joint areas [15,16], was observed in chronic dialysis patients who had been exclusively or predominantly haemodialysed with highly permeable, synthetic AN69 polyacrylonitrile membrane, compared with patients dialysed against cuprophan membrane.

We recently examined the hypothesis that the type of artificial membrane used for intermittent haemodialysis could be associated with a different prevalence of bone disease. We undertook a retrospective study in a large number of ureamic patients who were either dialysed with highly permeable, synthetic membrane (predominantly AN69 PAN membrane) or with cellulose membrane (cuprophan). We found that for similar plasma intact PTH values in the two groups, patients dialysed with cuprophan membrane had significantly greater osteoclast and osteoblast numbers in their bone biopsies than patients dialysed with synthetic membrane (Figure 2) [6]. This finding would be compatible with the more marked cytokine activation by cellulose than by synthetic membranes. We have now undertaken a prospective randomized trial to see whether we can confirm these retrospective findings.

Another approach to decreasing the incidence of dialysis amyloidosis-related pathologies could be the use of highly purified dialysis water (so-called ‘ultrapure’ water). A significant decrease in the incidence of carpal tunnel syndrome has been observed in chronic haemodialysis patients who were permanently dialysed with ultrapure dialysis water, supposed to be free of pyrogens, compared with patients dialysed against conventionally prepared dialysis water [17].

Symptomatic medical treatment of β₂-M amyloidosis

For the treatment of chronic arthralgias, standard analgesics may be helpful initially. Non-steroidal anti-inflammatory drugs (NSAIDs) are often the first choice of treatment, as they can effectively provide pain relief while minimizing the risk of adverse effects. However, in more severe cases, immunosuppressive medications may be necessary to control the disease process. These medications include glucocorticoids, which suppress the immune response, and disease-modifying antirheumatic drugs (DMARDs), which target specific molecules involved in the inflammatory response.

Fig. 1. Comparison of the β₂-microglobulin (β₂-M) removal that can be obtained by haemofiltration with highly permeable membrane (a) and by haemoperfusion using an adsorption column (b). Figure 1a shows the per cent reduction of the mean (±SEM) serum β₂-M level, corrected for haemoconcentration, and the amount of β₂-M found in filtrate during a polysulphone F60 haemodialysis (HD) or haemofiltration (HF) session in five uraemic patients (adapted from [3]). Figure 1b shows the reduction of serum β₂-M levels obtained in five individual haemodialysis patients either during a haemodialysis session using a combination of PMMA dialyser and haemoperfusion with β₂-M adsorption column (adapted from [7]).
Inflammatory drugs should be used with caution and only for short time periods because of the risk of gastrointestinal complications.

Colchicine is the drug of choice in the treatment and prevention of AA amyloidosis in patients with familial Mediterranean fever. In patients with chronic renal failure, no long-term experience is available with colchicine. Its neuromuscular toxicity and mediocre gastrointestinal tolerance in uremic patients probably restricts any use in the long term.

Intra- and periarticular glucocorticoid injection may be used for symptomatic management. However, because of their only transient effect, the usually polyarticular manifestations and the risk of infectious complications, this approach should generally be avoided.

Oral low-dose glucocorticoid administration is probably the best long-term therapy presently available, leading to a rapid and long-lasting improvement of joint pain. This has been shown in a recently conducted prospective, open trial in 27 chronic haemodialysis patients [18]. They were included in the study because of severe polyarticular arthropathy of amyloid nature and the lack of relief with standard analgesics. Twenty-three of the patients had undergone surgery of the median nerve(s) region because they had developed the carpal tunnel syndrome, and eight had evidence of destructive spondylarthropathy. The patients were administered oral prednisone at a daily dose of 0.1 mg/kg body weight. A dramatic improvement of the number of painful joints was seen in most patients, usually in less than 24 h. In 12 patients the treatment had to be stopped. In one patient, this was due to radiation synovectomy; in another there were concerns of glucocorticoid toxicity. Seven of the 12 patients died. The low-dose prednisone regimen was not suspected to be causally related to death in any of these profoundly debilitated subjects.

Thus low-dose daily oral glucocorticoid therapy has been shown to give significant improvement of osteoarticular pain in patients with dialysis-associated amyloidosis. However, the high rate of mortality under this treatment is a matter of concern. Therefore, a controlled, randomized prospective trial with this approach is urgently needed.

**Surgical treatment of β2-M amyloidosis**

In cases with severe amyloidosis-related complications such as the carpal tunnel syndrome and destructive arthropathy, orthopaedic surgery often is the only satisfactory solution. Arthroscopic synovectomy, bursectomy, cyst curettage and filling, resection of hypertrophied tendon sheaths, and of the coracoacromial ligament have been performed successfully in many cases. Thus, shoulder pain was relieved after endoscopic resection of the coracoacromial ligament in all subjects of a large series of 29 haemodialysis patients [19]. In another smaller series using the same technique, shoulder pain was relieved in three of four dialysis patients [20]. In many patients, however, major surgery is required, including total prosthetic joint replacement, repair of fractures and stabilization of spinal instability, to obtain relief and eventually cure of severely diseased joint pathology [21].

**Renal transplantation**

Finally, the successful transplantation of a kidney usually improves joint symptoms dramatically. It appears to halt the disease process, even though amyloid deposits probably cannot be resorbed [22] and even though moderate overproduction of β2-M appears to continue, compared with healthy subjects, probably as an expression of increased immune activation [23]. Radiologically visible erosive and cystic bone lesions persist for many years after successful renal transplantation [22, 24].

**New treatment perspectives**

As pointed out above, no specific medical treatment is available at present. An interesting novel approach is the recently reported attempt to inhibit amyloid formation by substances that might oppose the interaction between amyloid protein fibrils and basement membrane proteins, such as heparan sulphate proteoglycan, laminin, and collagen IV. Kisilevski et al. [25] synthesized low-molecular-weight, anionic sulphonate and sulphate compounds, with the goal to bring about an interference with amyloidogenesis *in vivo*. They
assessed the effect of poly(vinylsulphonate sodium salt) (PVS) in established mouse models of acute and chronic AA amyloidosis. When administered via the oral or intraperitoneal route, PVS was capable of virtually abolishing splenic AA amyloid deposition in the acute model, and arresting AA amyloid deposition in the chronic mouse model. These preliminary data in mice open promising new avenues for the treatment of all types of amyloidosis, including the β-M type. A word of caution is however required. Obviously it would be premature to extrapolate from such animal studies to the human setting. Detailed studies of the absorption, bioavailability, biodistribution, and toxicity characteristics of such compounds need to be done in animals before any use can be envisaged in humans. Nevertheless, we are confident that research efforts such as this one, based on pathogenetic considerations of the disease process, will eventually lead to the discovery of efficacious agents for the treatment and prevention of all types of amyloidosis, including the one which is associated with chronic renal failure.

References
