Reduction of circulating β2-microglobulin level for the treatment of dialysis-related amyloidosis

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Abstract
Dialysis-related amyloidosis (DRA) is a common complication associated with long-term haemodialysis therapy. The elimination of β2-microglobulin (β2m), the major constituent of the amyloid fibrils in DRA, from circulation has been expected to bring some clinical benefit. Recently, a direct haemoperfusion method using selective β2m absorption column to eliminate circulating β2m has been introduced into clinical practice. According to a recently performed, prospective, multicentre study, joint pain, stiffness and daily activities were significantly improved in patients with established DRA after the introduction of selective β2m absorption therapy. Meanwhile, although osteoarticular lesions progressed in the control group, there was no significant progression in the selective β2m absorption therapy group. The absorptive affinity of the column for β2m is not quite specific and therefore some other unknown uraemic toxins might be removed also. However, the improvement of joint pain and the ability to undertake daily activities showed reversed correlations against plasma β2m clearance. Symptoms associated with the increased amount of extracorporeal circulation and increased economical burden are areas of concern for this therapy. In conclusion, selective β2m absorption therapy was suggested to have the potential to ameliorate established DRA symptoms and simultaneously prevent its local development. The mechanism by which DRA symptoms are ameliorated remains obscure.

Introduction
Dialysis-related amyloidosis (DRA) is a common complication associated with long-term haemodialysis therapy [1]. There is no effective therapy to prevent and/or treat DRA. However, the elimination of β2-microglobulin (β2m), the major constituent of the amyloid fibrils in DRA that accumulate in uraemic patients [2], from circulation has been expected to bring some clinical benefit. Here we review such clinical attempts to eliminate circulating β2m in uraemic patients, as well as the clinical and pathophysiological significance of circulating β2m elimination as a part of DRA treatment.

Metabolism of β2m
β2m is generated at a constant rate, except in patients with systemic inflammation or cancer, and is eliminated from circulation under physiological conditions through the renal pathway. After being filtered by the glomerulus, β2m is degenerated in the proximal tubular cells through megalin-dependent reabsorption [3]. Thus, the plasma β2m level is elevated in patients with an impaired glomerular filtration rate. Although it is true that plasma or synovial fluid concentrations of β2m do not correlate with the incidence of DRA among dialysis patients [4], plasma accumulation of β2m is a universal finding in dialysis patients. Therefore, an elevated concentration of plasma circulating β2m should be a potential risk for the onset and/or development of DRA. In fact, amyloid fibrils are formed in vitro under very concentrated levels of native β2m without any proteolytic treatment [5]. Molecular modification of β2m was not required for the elongation of amyloid fibrils [6] in another recent in vitro amyloidogenesis system [7]. These findings strongly suggest that mere accumulation of β2m would play a promoting role for amyloidogenesis in uraemic patients.

It remains obscure whether established β2m amyloid fibrils are degenerated in vivo. However, β2m amyloid fibrils degenerated into monomeric or diametric forms of β2m in vitro [8]. Macrophages surrounding amyloid depositions are likely to scavenge amyloid fibrils in vivo.
[9]. Therefore, the suppression of amyloidogenesis by the elimination of β2m was expected to reduce the mass of deposited amyloid fibrils.

The outcome of renal transplantation on DRA

Plasma β2m levels decrease with improvement in DRA symptoms immediately after a successful renal transplantation [10]. Aggressive immunosuppressive therapy, but not improved β2m clearance, is regarded as playing a major role in this symptomatic relief through the suppression of local inflammation around amyloid depositions [11]. Whether bone lesions regress remains controversial [12,13], but relief of clinical symptoms persists even after withdrawal of corticosteroids. Residual β2m amyloid depositions in such bone cysts were found in a patient who received a renal transplant 10 years earlier [14]. This finding suggested that even sufficient elimination of circulating β2m is not capable of reducing the mass of amyloid deposition, at least over a period of 10 years. It remains unknown why relief of DRA symptoms persists in renal transplantation patients with residual amyloid depositions after the withdrawal of corticosteroid therapy. Unknown uraemic toxins might affect amyloid lesion, causing DRA symptoms, because symptomatic relapse has been found in those patients immediately after re-induction of haemodialysis therapy. Miyata et al. propose a role of AGE’s modification of β2m in triggering a local inflammation around the amyloid deposition [15]. However, whether the modification of AGEs on the remaining amyloid depositions disappears after renal transplantation therapy is still unknown.

Chronic haemodialysis and elimination of circulating β2m

Haemodialysis therapy using high-flux membranes show a superior reduction rate of circulating β2m than that using cuprophan membranes [16]. Peritoneal dialysis [17] and haemofiltration therapy [18], which generally remove a greater amount of middle-size molecules, demonstrate better rates of circulating β2m reduction than haemodialysis therapy. Since cuprophan membrane activates peripheral blood mononuclear cells [19] or lymphocytes [20] to release β2m into the circulation, even dialysis therapy using biocompatible-low flux membranes compared with cuprophan membranes kept the plasma β2m concentration of dialysis patients lower [21]. Polysulfon membranes directly absorb β2m to some extent [22].

Chronic haemodialysis therapy using a high-flux biocompatible membrane successfully delays the onset of osteoarticular symptoms associated with DRA when compared with that using a cuprophan membrane [23]. It is possible that high-flux biocompatible membranes prevent osteoarticular lesions through a decrease in circulating β2m levels. However, their better biocompatibility may play a greater role because cuprophan membranes promote the release of inflammatory cytokines from peripheral blood [24,25], which would contribute to the development of DRA [26].

Selective β2m absorption therapy

Recently, a direct haemoperfusion method using a selective β2m absorption column to eliminate circulating...
β2m has been introduced into clinical practice [27,28] (Figure 1). This selective β2m absorption column (Lixelle, Kanegafuchi Kagaku, Takasago, Japan) is directly connected to the standard haemodialysis circuit to selectively remove circulating β2m [29] (Figure 2). Besides improving the β2m reduction rate, a case of carpal tunnel syndrome demonstrated remission after the application of this selective β2m absorption therapy [30].

According to a prospective multi-centre study performed by a Japanese group, joint pain, stiffness, and the ability to perform daily activities were significantly improved in patients with established DRA after the introduction of selective β2m absorption therapy, and this improvement lasted >12 months. Meanwhile, although the osteoarticular lesions demonstrated on bone X-ray progressed in the control group, there was no further significant progression in the selective β2m absorption therapy group. Thus, selective β2m absorption therapy was suggested to have the potential to ameliorate established DRA symptoms and simultaneously to prevent its local development.

As described previously, factors other than circulating β2m reduction play an important role in the relief
of DRA symptoms after transplantation and during haemodialysis therapy, using a high-flux biocompatible membrane. However, removal of β2m is currently the only reasonable candidate to achieve the clinical improvement by Lixelle treatment. It is true that the absorptive affinity of the Lixelle column for β2m is not quite specific, and therefore some other unknown uraemic toxins might be removed by this column as well. However, the improvement of joint pain and the ability to perform daily activities showed an inverse correlation with the plasma β2m clearance. Selective β2m absorption therapy may perform a mere reduction of circulating β2m to relieve DRA symptoms.

There are some problems concerning selective β2m absorption therapy. First, low blood pressure during haemodialysis and/or progression of anaemia are sometimes observed with this therapy because of the increased amount of extracorporeal circulation. Secondly, since selective β2m absorption therapy is a symptomatic therapy, it must be performed as long as the haemodialysis therapy continues. Consequently, increased economic burden becomes another problem. Medicare covers selective β2m absorption therapy for 1 year in Japan. Therefore, it is practically impossible to continue this therapy for >1 year, and thereafter all those patients are forced into a symptomatic relapse of DRA. Thus, selective β2m absorption therapy is at present not yet widely accepted in clinical practice.

Conclusion

It is likely that the elimination of circulating β2m ameliorates the symptoms caused by DRA, as well as preventing its further development. On theoretical grounds, elimination of circulating β2m was originally expected to prevent amyloidogenesis and decrease the amount of amyloid deposition. However, there is no evidence of amyloid reduction, although both the subjective and objective clinical symptoms associated with DRA were obviously improved by those treatments. Major osteoarticular symptoms associated with DRA are not directly caused by amyloid deposition but are largely ascribed to the inflammatory reaction caused by macrophages infiltrating around the amyloid deposition [31]. Therefore, it is possible to assume that the elimination of circulating β2m plays some direct role in regulating inflammation around amyloid deposition, through a mechanism independent from the inhibition of amyloidogenesis. In fact, we found macrophages infiltrating around amyloid deposits specifically assimilating circulating β2m in the tissue samples obtained from dialysis patients [32] (Figure 3).
β2-microglobulin reduction for amyloidosis treatment

If the inhibition of β2m assimilation prevents the activation of those macrophages, the clinical significance of circulating β2m elimination therapy must be re-evaluated.

References

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