

Immunosuppressive treatment in dialysis patients

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Abstract

Immunosuppressive treatment is a critical procedure in dialysis patients, in whom an increased risk of infection is already present. Haemodialytic treatment increases the patient's susceptibility to bacterial infection, mainly by impairing polymorphonuclear leukocyte phagocytosis, but it can also restore the patient's immunological defences by improving the T-cell function, which is reduced by pre-dialysis uraemia. Patients on dialysis usually continue the immunosuppressive treatment that had been established for the illness that caused their renal failure [e.g. systemic lupus erythematosus (SLE) or renal vasculitis]. Less frequently, patients on dialysis need immunosuppression for immunological or inflammatory diseases that appear '*de novo*' after initiation of dialysis. SLE and antineutrophil cytoplasmic antibody (ANCA)-related vasculitides are immunological illnesses that frequently cause end-stage renal failure (ESRF). A reduction in serological and/or clinical activity is usually observed in SLE patients after they reach ESRF, but a similar or increased frequency of extrarenal relapse episodes in lupus patients after the beginning of the dialysis, compared with the pre-dialysis period, has also been described. Frequency of relapse episodes in patients on dialysis treatment for ANCA-related vasculitides varies from 10 to 30% per patient/year in different reports, and it is higher than the frequency of relapses after renal transplantation; anti-rejection therapy seems to be the most likely protective factor in these conditions. The treatment of relapse episodes in SLE or ANCA vasculitis in dialysis-dependent patients is usually not different from treatment of relapses in patients with dialysis-independent renal function. However, the risk of severe infection caused by immunosuppressive treatment is relevantly higher in dialysis patients. Furthermore, there is a lack of prospective controlled studies indicating the optimal

management of immunosuppressive protocols in dialysis patients. A particularly careful assessment of the patient's risks and benefits is necessary in deciding how long immunosuppressive treatment should last after acute or rapidly progressive renal damage, that should require dialysis treatment, in patients with SLE or ANCA vasculitis. In the above conditions, the risks of prolonging immunosuppressive treatment must be balanced against the relatively good prognosis offered to these patients by dialysis and renal transplantation. In a retrospective review of 24 patients receiving long-term steroid therapy (> 3 months) in our dialysis unit in the past 5 years, we found relevant clinical differences in the patients receiving steroid treatment compared with 24 controls. Steroid-treated patients showed less favourable nutritional conditions, with lower serum albumin and body mass index *vs* non-steroid-treated patients; moreover, C-reactive protein values were persistently higher in the steroid-treated group. Steroid treatment in these patients was usually performed at the beginning of regular dialysis, as a continuation of the treatment that started before the initiation of dialysis. Only two patients, who needed a prolonged low-dose steroidal treatment to control a malnutrition–inflammation–atherosclerosis (MIA) syndrome, started steroids many years after beginning dialysis. Steroid treatment was effective in improving the nutritional condition and inflammatory symptoms in these two patients after all conventional measures had failed.

Keywords: ANCA vasculitis; haemodialysis; immunosuppressive therapy; MIA syndrome; renal graft failure; SLE

Introduction

The management of immunosuppressive therapy in dialysis patients is a difficult matter: infection leads to a high incidence of complications among uraemic patients on dialysis, in whom the immune system

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appears deranged to various degrees (Table 1). Alterations in the neutrophil function, e.g. phagocytosis, mononuclear cell activation, T-cell function and adhesion molecule expression, have been well documented in uraemic patients [1]. Dialysis accesses are an additional source of infection as they are an easy route of penetration of bacteria into the bloodstream or the peritoneal cavity [2]. Furthermore, dosing of immunosuppressive drugs in dialysis patients is difficult, since uraemia and the dialysis sessions interfere with the metabolism of some immunosuppressive drugs [3].

Haemodialysis impairs the function of neutrophil leukocytes, which are the main cells of the specific defence system during bacterial infections. Iron overload, high intracellular calcium and uraemic toxins are considered the main cause of neutrophil dysfunction [4].

Conversely, the initiation of dialysis treatment leads to an improvement in the T-cell function [5]; this could explain the higher rejection rate observed in patients who received a renal transplantation after starting dialysis *vs* those who received a pre-emptive renal transplantation [21].

Immunosuppression is a risk factor for peritonitis in peritoneal dialysis patients [22]. An impaired outcome of continuous ambulatory peritoneal dialysis (CAPD) treatment in immunosuppressed patients has been described. Cameron *et al.* reviewed the outcome of all patients who started a peritoneal dialysis treatment in the same year at a single centre [23]. They compared 39 patients who started peritoneal dialysis while they were on immunosuppressive treatment for different reasons with 146 patients on peritoneal dialysis without immunosuppression. The immunosuppressed patients had a higher incidence of peritonitis [69 episodes in 39 patients, *vs* 99 episodes in 146 patients ($P < 0.001$)]. Hospital admissions and laparatomies for catheter removal were significantly more frequent in immunosuppressed patients. The authors concluded that CAPD might not be the initial therapy of choice in these patients.

Clinical setting in which immunosuppressive treatment is given to dialysis patients

Usually patients on dialysis receive immunosuppressive treatment for the same disease that caused their renal failure. Less frequently, an immunosuppressive treatment is started *de novo* after the beginning of regular dialysis (RD). Systemic lupus erythematosus (SLE), systemic vasculitis and multiple myeloma are the main conditions in which the need for immunosuppression may persist during RD, because of their frequent systemic involvement. Another common condition in which immunosuppression is continued after starting dialysis is the treatment of patients with acute or chronic renal failure after kidney transplantation.

Lupus erythematosus

A reduction in serological and clinical activity after the initiation of RD has been reported in SLE patients, but an increased extrarenal relapse rate has also been reported.

Mojcik *et al.* found that the prevalence of patients with clinical lupus activity in the post-dialysis period diminished over time: 55, 6.5 and 0% after 1, 5 and 10 years, respectively. They found that the serological activity in lupus was not necessarily correlated with clinical activity and that it was a more frequent condition present in 80, 60 and 22% of the patients after 1, 5 and 10 years, respectively. The causes of this phenomenon are not completely understood [24].

In a retrospective study, Szeto *et al.* reviewed systemic manifestations, serological profile and treatment of 18 lupus patients who received RD from 1987 to 1996 (mean follow-up duration 43 ± 3.7 months). Nine patients experienced 32 lupus flare-ups (62%; 0.3 episodes per patient-year) within the first year of dialysis. Compared with the nine patients who had no flare-ups, the patients with flare-ups were younger (24 *vs* 32 years; $P < 0.05$), were more likely to have a history of seizures ($P < 0.05$), and had fewer episodes of serositis and vasculitis in their past history [25].

In a retrospective study carried out in 19 patients, Krane *et al.* found that most patients with SLE and end-stage renal disease (ESRD) continued to show evidence of disease activity: there were seven haemodialysis patients, five peritoneal dialysis patients and seven transplant recipients in the study population. Clinical events recorded to evaluate disease activity were malar rash, ulcers, alopecia, arthritis, myositis, pleuritis, pericarditis, fever, cerebritis and vasculitis. Disease activity was measured using the SLE disease activity index and the requirement for immunosuppressive medications. Serological studies showed little change in the dialysis patients before and after ESRD; however, there was a tendency for lupus serological results to improve after transplantation. When all events were combined, there was a significant, greater incidence of lupus activity after both haemodialysis and peritoneal dialysis ($P < 0.01$), but not after renal transplantation. Fifty-eight percent of the patients undergoing dialysis died during a 5-year follow-up; all had clinically active lupus. It is noteworthy that 84% of the patients included in the study were black women, who represent a subgroup of lupus patients in whom the disease is more likely to remain active after development of ESRD [26].

Treatment of lupus flare-ups in patients on RD is directed against the extrarenal manifestations. In the acute phase of SLE, most patients require dialysis for acute or rapidly progressive renal failure. A basic rule of prudence in treating these patients is to avoid too strong and/or too prolonged immunosuppression in the attempt to recover renal function, especially in the case where previous renal histological evaluation showed diffuse severe renal lesions that were unlikely to recover. In these situations, one must consider that

Table 1. Abnormalities of immune system in uraemic and haemodialysis patients

Type of immune derangement	Altered immune function(s)	Cause	Clinical manifestation(s)
Unspecific defence system: ↓PMNL functions	↓Chemotaxis ↓Phagocytosis* ↓Intracellular killing by proteolytic enzymes* ↓Toxic oxygen radicals ↓Inhibition of degranulation	Iron overload ↑Level of intracellular calcium ↑Endogenous glucocorticoid levels Bioincompatible dialysis membranes Ubiquitin (in CAPD patients) <i>p</i> -Cresol Uraemic toxins: granulocyte-inhibiting protein→ GIP-like Ig light chains; GIP-like β_2 -microglobulin; angiotensin; complement factor D	↑Susceptibility to bacterial infections
Specific defence system: Deficient response of T-lymphocytes	↓T-cell response to phytohaemagglutinin (<i>in vitro</i>)** ↓Delayed-type hypersensitivity** ↑IL-12 Imbalanced T-cell activation Lymphopenia ↓NK cell function ↓Plasma level of IL-6 ↓Release of IL-6 and IL-10 (<i>in vitro</i>) TNF- α and s-TNF- α receptors 1 and 2 Low response to vaccination ↓Levels of specific Abs after HBV vaccination ↓Immunization to tetanus toxoid*** Hypogammaglobulinaemia	Selenium deficiency Zinc deficiency Bioincompatible dialysis membranes Ageing	↓Resistance to viral infections ↑Incidence of malignancy
Depressed specific antibody production		↓T cell-dependent antigen	↓Responsiveness to vaccines
Reduced levels of Igs		↑Urinary leaking in nephrotic syndrome	↑Susceptibility to bacterial infections
Complement system: Activation of alternative pathway of complement	Neutrophil activation and sequestration in pulmonary circulation and infiltration in other organs ↓Cellular immunity ↑Urinary leaking in nephrotic syndrome	Free hydroxyl groups on the cellulosic dialysis membrane	First use syndrome
↑Level of complement		↑Susceptibility to bacterial infections	

The table shows a summary of the main immune dysfunctions in uraemia and haemodialysis patients with the specific altered immune function, the underlying cause and the clinical manifestations. The data are summarized from original papers [references 4–20].

*Improvement by cefonocid therapy; **improvement after initiation of haemodialysis and after IV calcitriol therapy; ***increased by rEPO therapy.

↓Reduced activity or synthesis; ↑enhanced activity or synthesis [references 4–20].

dialysis and renal transplantation offer a reasonable survival, while if immunosuppression is too strong and for longer than 1 or 2 months, it increases mortality [27].

ANCA-related vasculitis

Fifty to eighty percent of the patients requiring dialysis in the acute phase of microscopic polyarteritis or Wegener's granulomatosis recover sufficient renal function to come off dialysis [28,29].

A prospective trial demonstrated that plasma exchange added to steroids and cyclophosphamide therapy is likely to improve renal function in patients with antineutrophil cytoplasmic antibody (ANCA)-related vasculitis who became dialysis dependent [30,31].

Different rates of relapse of vasculitis have been described by different authors, ranging from 0.1 to 0.3 episodes per patient/year [32,33]. Relapse rates are higher in dialysis than in transplanted patients. Relapses usually respond to steroids and cyclophosphamide treatment at the usual dosage. Frequent misdiagnoses, leading to wrong or late treatment, have been described in these situations, e.g. an intestinal vasculitis mimicking peritonitis in a CAPD patient, and a pulmonary haemorrhage mimicking pulmonary oedema in haemodialysis patients. Relapses are more frequent in dialysis patients than in transplanted patients, and in more patients with Wegener's granulomatosis than in patients with microscopic polyarteritis [32].

In a retrospective analysis of 35 patients with Wegener's granulomatosis on RD with an average follow-up of 43 months, Haubitz *et al.* [33] described a patient's actuarial survival of 93 and 79% at 2 and 5 years, respectively. They observed 29 relapse episodes in 17 patients (0.27/patient/year); two-thirds of the relapses appeared during steroid therapy and one-sixth during cyclophosphamide therapy. No relationship was observed with the use of different dialysis membranes. The authors concluded that maintenance immunosuppression regimens are usually insufficient to cover relapses in Wegener's granulomatosis, but they may increase the risk of infection and malignancies.

Dialysis-related β_2 -microglobulin amyloidosis

Patients treated by long-term maintenance haemodialysis frequently develop a form of chronic arthropathy that is strongly associated with β_2 -microglobulin amyloid deposition and related to β_2 -microglobulin retention. Renal transplantation appears to arrest, at least in part, the progression of β_2 -microglobulin, but it neither leads to dissolution of the deposits nor prevents progression of the destructive arthropathy. Most symptoms caused by amyloid deposition are probably improved as a result of corticosteroid therapy [34].

Some clinicians administer low dose steroids (5–10 mg daily) in haemodialysis patients with severe arthralgia due to β_2 -microglobulin deposition [35]. Our protocol is to administer a single 10–20 mg pulse dose of intravenous dexamethasone, as induction therapy, followed by oral prednisone, 5–10 mg in a single daily dose, or on alternate days, as maintenance therapy. These patients usually require long-term treatment that could lead to long-lasting morbidity for bone fractures and spontaneous tendon ruptures that should be prevented by better supervision and treatment of hyperparathyroidism and other bone diseases, usually present in dialysis patients [36].

Immunosuppression in patients returning to dialysis after renal transplant failure

When patients restart dialysis treatment after transplant failure, they usually need to continue some immunosuppressive treatment to avoid precipitation of rejection, secondary adrenal insufficiency and other potential adverse immunological effects due to the rapid withdrawal of immunosuppression. Usually, cyclosporin and tacrolimus are rapidly suspended in this condition, because of the risk of neurotoxicity [37], while steroid treatment is continued in progressively tapered doses for weeks or months.

Transplant nephrectomy is a condition associated with high morbidity and some mortality. In 1048 renal transplants performed between 1971 and 1990, O'Sullivan *et al.* reported that 8.2% of all transplanted patients required transplant nephrectomy, which caused complications in 60% of the cases: 20% were major complications, four of them lethal. Major complications were more frequent in the presence of acute rejection. Nephrectomy occurrence increased when cyclosporin was introduced ($P < 0.05$) [38].

Continuation of immunosuppression after the start of dialysis treatment is often necessary to control the symptoms related to rejection, more frequently in patients with early graft failure, but the practice should be restricted to a short time. Gregoor *et al.* compared the outcome of patients who received a continuation of low-dose immunosuppression after a failed renal transplantation with that of patients who did not receive any immunosuppression in the same conditions. Notwithstanding a higher occurrence of transplantectomy, the non-immunosuppressed patients showed a more favourable outcome, with a lower infection rate (0.68 vs 2.28 episodes/patient/year). The odds ratio for severe infection was 14.2 times higher in immunosuppressed patients. The five patients who died had received immunosuppression during dialysis treatment [39].

The most frequent complications associated with immunosuppression withdrawal after failed renal transplantation are precipitation of the rejection requiring immediate transplantectomy [40], secondary adrenal insufficiency [41], reactivation of a smouldering immunodisease [42] and potential sensitization to HLA antigens [43].

Table 2. Characteristics of patients who received steroid treatment vs control patients

	Steroids	No steroids	P-value
Age	57.52 ± 15.19	58.22 ± 15.1	0.97
Years on dialysis	9.89 ± 5.91	8.05 ± 4.8	0.34
Rate of hospitalization days/patient/year	8.86	4.2	0.05
Serum albumin	3.45 ± 4.03	3.77 ± 0.406	0.013
Haemoglobin	8.82 ± 6.19	9.03 ± 1.68	0.65
C-reactive protein	4.38 ± 6.19	1.67 ± 1.85	???
Kt/V	1.27 ± 0.29	1.24 ± 0.21	0.66
Body mass index	21.52 ± 2.07	24.07 ± 3.73	0.025

Main clinical and laboratory data of 22 haemodialysis patients in our unit who received permanent steroid therapy with or without immunosuppressive agents and of 22 haemodialysis patients who did not receive steroids or immunosuppression. The two groups are homogeneous for age, sex, co-morbidity and duration of haemodialysis treatment. See text for details.

There are neither prospective studies nor definite protocols for the tapered withdrawal of steroids and immunosuppressants in patients on dialysis after renal transplant failure. Some clinicians prefer to withdraw cyclosporin and azathioprine first, while others prefer to stop the steroids first.

The most widely used policy is immediate withdrawal of immunosuppression and pre-emptive nephrectomy in patients with early graft failure in order to avoid acute rejection. In the case of late allograft failure, cyclosporin, mycophenolate mofetil or azathioprine are usually stopped immediately, and prednisone is tapered by 1–2 mg/month until it is stopped. Symptoms of allograft rejection are carefully monitored. In the case of rejection, a 5–7 day course of steroids, at the dose of 0.5–1 mg/kg, is given. If symptoms persist or rejection recurs, the patient is referred to surgery for transplantectomy [44]. The symptoms of steroid withdrawal are also monitored. A reactivation of a multisystem disease, e.g. sarcoidosis, after withdrawal of immunosuppression after failed renal transplantation has also been described [42].

Retrospective study of patients who received immunosuppression during dialysis treatment

In the following retrospective survey, 150 patients who received dialysis treatment in the past 6 years in our dialysis unit are reviewed. Twenty-two patients who received permanent steroid therapy, for at least 3 months with or without other immunosuppressants, were included in the present survey. A control group of dialysis patients who did not receive immunosuppression was selected among dialysis patients of the same age, gender, co-morbidity and duration of dialysis treatment (Table 2). The haemodialysis patients received immunosuppression for the following reasons: ANCA vasculitis in seven cases, SLE in five, failed renal transplant in five, malnutrition–inflammation–atherosclerosis (MIA syndrome) in two, and familial Mediterranean fever in one case. Serum albumin

values were significantly lower in the dialysis patients who received immunosuppression compared with controls. In Figure 1, it can be seen that serum albumin values were higher in both groups of patients in the following 2 years, but remained significantly lower in the immunosuppressed patients ($P < 0.049$). Figure 2 shows the outcome of C-reactive protein (CRP) values in immunosuppressed vs non-immunosuppressed patients during a 7-year follow-up. Average CRP values were significantly higher in patients who received immunosuppression, and dropped in the subsequent follow-up, reaching normal values only after many years of dialysis.

Steroid treatment was usually performed at the beginning of the dialysis treatment in all groups of patients. Only patients with the MIA syndrome started steroid treatment after being treated on dialysis for many years. The MIA syndrome appeared with severe malnutrition, myalgia and fever, leading to a progressive serious deterioration of the patient's condition, requiring long-term hospitalization. The symptoms of the above patients mimicked a rheumatic polymyalgia, and responded well to long-term low-dose steroid treatment.

Figure 3 shows the outcome of one of these patients. This was a 72-year-old female on haemodialysis for 20 years who had been admitted to our unit for fever, malnutrition, arthralgia and advanced atherosclerosis.

A complete work-up, including an echocardiographic study, did not demonstrate any evidence of infection or malignancy. The patient was very ill and anorexic, and was unable to walk. During the fourth week of admission, she underwent a total body computed tomography (CT) scan, preceded by steroid prophylaxis (prednisone, 150 mg) to prevent anaphylactic reactions as she was allergic. After prophylaxis, the patient's condition improved suddenly, fever remitted and CRP decreased in the following days.

After 1 week, fever reappeared and the patient's general condition worsened again. She was treated with dexamethasone 20 mg i.v., followed by oral prednisone, 10 mg/day as maintenance: her fever

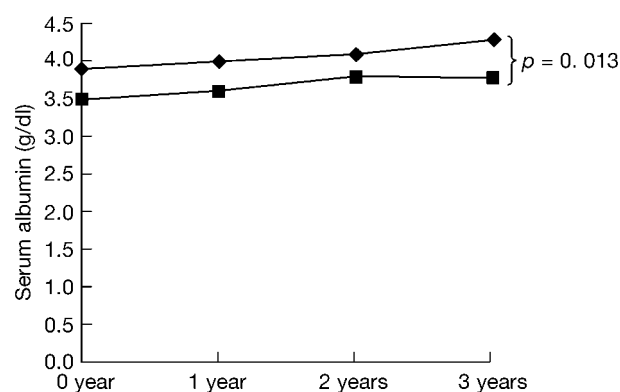


Fig. 1. Serum albumin values of 22 haemodialysis patients who received permanent steroid therapy with or without immunosuppressive agents and of 22 haemodialysis patients who did not receive steroids or immunosuppression. Serum albumin was higher in both groups of patients in the following 2 years, but remained significantly lower in the immunosuppressed patients ($P < 0.049$).

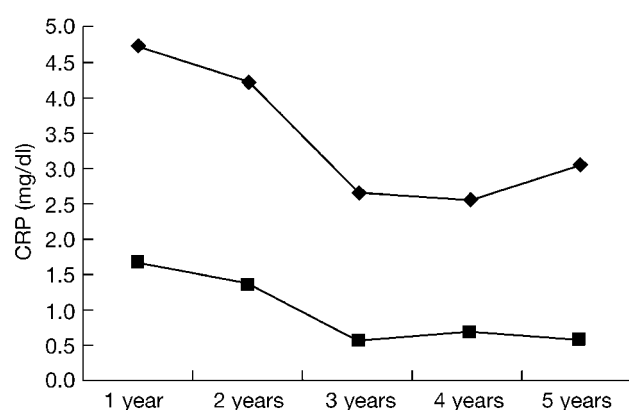


Fig. 2. The evolution of C-reactive protein (CRP) values in 22 immunosuppressed vs 22 non-immunosuppressed haemodialysis patients during a 5-year follow-up. Average CRP values were significantly higher in patients who received immunosuppressive therapy.

disappeared, her nutritional status improved, and her CRP and albumin values normalized in a few weeks; She was discharged in an improved nutritional condition.

Discussion and conclusions

Immunosuppressive treatment lasting at least 3 months in patients on chronic dialysis is a frequent finding. Twenty-four out of 250 patients on dialysis treatment in our unit in the past 5 years had received such treatment. Furthermore, an additional 10% of our dialysis patients received a short course of steroid therapy, mainly to relieve arthralgia due to amyloid deposition or to treat or prevent allergic reactions. Unfortunately, there are no controlled studies indicating the best schedule for immunosuppressive therapy in dialysis patients. We can only resort to a review of a few sparse, uncontrolled studies to gather some ideas that might be useful in the clinical practice of immunosuppression in patients on RD treatment.

The risks and the difficulties in managing steroidal and immunosuppressive therapy are higher in dialysis patients than in patients with a dialysis-independent renal function for the following reasons.

- (i) The different metabolism of some immunosuppressive drugs in patients with renal failure. Some drugs, such as methotrexate, are totally contra-indicated in the presence of advanced renal failure [45]; other drugs, such as azathioprine and cyclophosphamide, are metabolized preferentially by the liver, but are a potential cause of major myelotoxicity due to retention of toxic metabolites, which accumulate in uraemia. In common practice, immunosuppressive drugs are used frequently in a relatively safer condition as steroid-sparing agents, especially in maintenance treatment. In the treatment of dialysis patients, there is the tendency

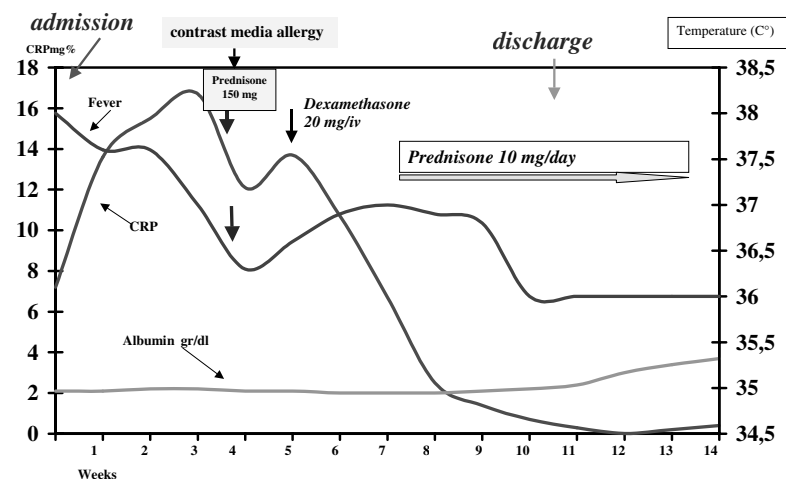


Fig. 3. The evolution of a 72-year-old female on haemodialysis for 20 years who had been admitted to our unit with fever, malnutrition, arthralgia and advanced atherosclerosis (MIA syndrome). A complete work-up, including an echocardiographic study, did not demonstrate any evidence of infection or malignancy (for details, see text).

to use steroids as a monotherapy to maintain immunosuppression; this practice may require a higher steroid dosage and can lead to further steroid side effects.

- (ii) The presence of conditions which '*per se*' cause a decreased resistance to bacterial infections in dialysis patients, such as the presence of vascular access or a peritoneal catheter; for the latter condition, peritoneal dialysis is not the treatment of choice in immunosuppressed patients, since it can increase the incidence of severe infections leading to high mortality [23].

Particularly critical is the management of patients who undergo dialysis treatment for rapidly progressive or acute renal failure caused by glomerulonephritis or vasculitis. In these conditions, immunosuppressive therapy is continued in an attempt to recover renal function and is usually a full dose of steroids and other immunosuppressive agents (more frequently cyclophosphamide is applied). The risk of complications of severe infections and mortality in these situations is high. A careful assessment of the patient's risks and benefits is crucial in deciding on the intensity and duration of the immunosuppressive treatment in these conditions, especially in elderly and high-risk patients. This decision frequently is needed in SLE or ANCA vasculitis patients who need dialysis for acute or rapidly progressive renal failure. It should be taken into consideration that dialysis and renal transplantation offer satisfactory survival in these patients [24,28].

The maintenance treatment of patients on dialysis for lupus nephritis or ANCA-related vasculitis in the attempt to prevent relapse episodes is a major though controversial problem. It is believed traditionally that a reduction of serological and clinical activity in patients with SLE after starting dialysis treatment is the most frequent condition, but an accurate review of the modern literature does not confirm this finding [25,26].

An increased frequency of extrarenal episodes of SLE has been reported in these patients after starting dialysis therapy. Moreover, in patients with ANCA vasculitis, the occurrence of acute extrarenal relapse is a relatively frequent condition, observed in 10–30% of cases during RD [28,29].

The concept that dialysis treatment may '*per se*' cause an immunosuppressive action is seldom observed in clinical practice. On the contrary, an improvement of the patient's immunological reactions, such as T-lymphocyte function, after starting dialysis treatment as compared with a pre-dialysis period, has been described. Improvement of the T-lymphocyte function is the most likely cause of the higher frequency of acute rejection episodes observed in patients undergoing renal transplantation after starting dialysis treatment compared with patients undergoing pre-emptive renal transplantation [21].

The increased risk of infections and mortality suggests prudence in managing immunosuppressive

treatment in patients restarting dialysis after graft failure. In this situation, immunosuppressive therapy is often necessary to avoid urgent transplantectomy for acute rejection. Moreover, since occult adrenal hypocorticism frequently is present in these patients, steroids should be tapered slowly, especially in the case of long-term duration of the transplant function [40–42].

Continuing long-term immunosuppression in patients on dialysis for transplant failure in an attempt to keep some residual renal function is not indicated as it causes severe infection and a high mortality [39].

A review of the outcome of 24 patients who received long-term steroid therapy in our dialysis unit shows some interesting clinical features: steroid-treated patients had a lower body mass index than control patients; serum albumin values were significantly lower in steroid-treated patients and persisted at a lower level for years compared with the control group. An inverse outcome was observed for serum CRP values, which were higher and persisted for many years in steroid-treated patients.

The improvement in two of our patients with the MIA syndrome after long-term steroid treatment deserves further comment. Probably, steroid treatment was a difficult choice in these two patients, because of the presence of overt malnutrition, a high risk of infection and lack of evidence in the literature that such patients may benefit from steroid therapy. However, the results with steroid therapy in these patients were very encouraging. It is our present policy to reserve steroid treatment in MIA syndrome patients only for those with severe dialysis inflammation, who are unresponsive to conventional treatment, and in whom the presence of infection and/or malignancies has been thoroughly excluded, and all conventional attempts to restore normal nutrition have failed.

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