Therapeutic Apheresis and Dialysis
7(2):155–160, Blackwell Publishing, Inc.

Indications of Plasma Exchanges for Systemic Vasculitides

Loïc Guillevin and Christian Pagnoux

Department of Internal Medicine, Hôpital Avicenne, Université Paris-Nord, Assistance Publique–Hôpitaux de Paris, Bobigny, France

Abstract: Indications of plasma exchanges for systemic vasculitides are well delineated according to the results of therapeutic trials undergone during the past decades. In combination with antiviral agents and/or immunosuppressants, plasma exchanges appear to be essential in the treatment of HBV-related polyarteritis nodosa; pauci-immune glomerulonephritis, kidney-limited or as a feature of Wegener's granulomatosis or microscopic polyangiitis; Goodpasture's syndrome, and for some complications of cryoglobulinemia. In patients with HIV and HBV-associated vasculitides, for which immunosuppressants are deleterious, plasma exchanges are also helpful and have been shown to be effective, combined with an antiretroviral regimen. In polyarteritis nodosa without HBV infection, Wegener's granulomatosis, Churg–Strauss syndrome and in other systemic diseases vasculitides, plasma exchanges can help to control or attenuate the disease. We review herein these indications of plasma exchanges in the light of the results of major trials. **Key Words:** Plasma exchange—Polyarteritis nodosa—Rapid progressive glomerulonephritis—Vasculitides—Viral infection.

Plasma exchange (PE) is used in a wide variety of vasculitides but PE should be prescribed precisely, according to the disease diagnosed and its severity. The time to prescribe PE, the choice of combined therapy and session scheduling can differ from one vasculitis to another.

Plasma exchange cannot be prescribed as the sole treatment and is more frequently part of a therapeutic strategy. Herein, we review the main indications of PE in light of the results of retrospective and prospective trials.

POLYARTERITIS NODOSA AND CHURG–STRAUSS SYNDROME

For several decades, an overall improvement of the prognoses for polyarteritis nodosa (PAN) and Churg–Strauss syndrome (CSS) have been observed as a direct consequence of the systematic use of corticosteroids (CS) and extensive use of cyclophosphamide (CYC) (1–4). In the early 1980s, PE was widely prescribed to treat PAN (5–8). Because PE is able to remove immune complexes and improve the capacity of the reticuloendothelial system to clear these complexes (9), PE was effective and was able to successfully treat patients with PAN related to hepatitis B virus (HBV) (7) and to improve the course of PAN after failure of CS and CYC (6).

When we decided to conduct prospective therapeutic trials in PAN and CSS patients, two major concerns were the indications of PE and the specific antiviral treatment for HBV-related PAN.

The results of the first protocol (10) showed that 10-year survival rates for patients treated with CS and PE, and those treated with CS, CYC and PE did not differ, despite better disease control in the group that received CYC as the first-line treatment and more relapses in the CS and PE group. These results did not enable us to conclude in terms of survival as to the superiority of CYC over the other treatment but clearly showed that disease control is much better with CYC in combination with CS and PE than without them.

Since 1984 we have treated HBV-related PAN differently than PAN without HBV markers or CSS. It should be emphasized that, in HBV-related PAN, long-term CS therapy can at best stabilize the disease and that relapses might occur later. Concerning the evolution of patients with and without HBV markers,

Received January 2003.
Address correspondence and reprint requests to Dr Loïc Guillevin, Department of Internal Medicine, Hôpital Avicenne, Université Paris-Nord, Assistance Publique–Hôpitaux de Paris, Upres 3409, 125 rue de Stalingrad and Université Paris-Nord, 93009 Bobigny, France. Email: loic.guillevin@avc.ap-hop-paris.fr

we observed that 1-year survival rates were poorer for patients with HBV-related PAN because of a higher rate of lethal digestive system complications. At 5 years, rates did not differ significantly for the two groups but 5/15 survivors from the group with HBV markers developed chronic liver disease (10).

We established a specific protocol giving the indications of PE to treat PAN without HBV markers and CSS (11). Our purpose was to evaluate whether this regimen was able to improve disease control and the survival rate. We demonstrated that, for the patients who underwent PE, the outcome was not better and was not significantly different from that of those who took CS alone. The failure of these therapeutic strategies to control disease activity was observed more often than in our previous study, in which CYC had been given initially in combination with CS and/or PE. In contrast, lethal infections associated with the regimen were rare in this later study (1 patient) and the survival rate was higher than that seen in other studies including our earlier one: 83 versus 75% at 7 years. Fourteen patients required oral CYC for 1 year and dapsone was given to two others. These drugs were able to control the disease in most cases without exposing the patients to iatrogenic risk.

We have also tested indications of PE in a subgroup of patients with severe PAN without HBV infection or with CSS. Severity was assessed using the five-factors score (FFS) (12). The FFS comprises the following items: classes of serum creatinine levels (≤1.58 and >1.58 mg/dL) and proteinuria (≤1 and >1 g/day), presence of severe gastrointestinal (GI)-tract involvement, cardiomyopathy, and/or central nervous system (CNS) involvement (12). Plasma exchange did not improve the prognosis for this group of patients but did facilitate control of the disease. We think that PE should be prescribed only for vasculitides failing to respond to CS and CYC, and should not be prescribed as the initial treatment for this subgroup of vasculitides. Careful assessment of the indications of PE in subgroups of patients with specific symptoms (i.e., mononeuritis multiplex, nephropathy, GI involvement) has not yet been performed but could define more precisely the indications for PE in vasculitides.

In HBV-related PAN, PE is indicated and is the most effective treatment (13). In this context, we proposed a regimen of vidarabine (Vira A) and PE after short-term prednisone administration (2 weeks). This therapeutic sequence was proposed to obtain the following effects: initial administration of CS to quickly control the most severe, life-threatening manifestations of PAN which are common during the first weeks of the disease; rapid discontinuation of CS in order to trigger a rebound of immunological clearance of HBV-infected hepatocytes and favor seroconversion from HBe antigen (Ag) to anti-HBe antibody (Ab), as documented for chronic hepatitis B; and PE to remove pathogenic circulating immune complexes and prevent further damage, especially after CS discontinuation.

When the study began (14), Vira A was the most effective antiviral treatment available against HBV. Indeed, it was demonstrated that Vira A was able to induce HBeAg to anti-HBeAb seroconversion in nearly half of the patients with chronic hepatitis and we expected to obtain similar or better results in HBV-related PAN. The overall therapeutic results obtained in this group of patients were excellent: 77% of the patients no longer had any symptoms of vasculitis following therapy and none relapsed during the prolonged follow-up period. After the first cycle of Vira A, 12/33 (36.4%) patients seroconverted from HBeAg to anti-HBeAb and seroconversion from HBsAg to anti-HBsAb was obtained in five (15%) patients. A second course of antiviral therapy (Vira A or interferon-alpha 2b) was able to increase the HBeAg to anti-HBeAb seroconversion rate to 45.4%. Two other patients, who underwent a second cycle of Vira A administration, no longer had detectable circulating HBeAg and no longer expressed serological evidence of replication, as assessed by HBV-DNA spot hybridization, but they still do not produce anti-HBeAb. HBV replication is no longer detectable in the sera of 17 (51.5%) patients. In most cases, seroconversion was obtained within a few weeks after stopping the treatment but, in five patients, it occurred more than 1 year after the end of the Vira A and PE cycle. In two patients, HBeAg to anti-HBeAb seroconversion was obtained 24 months after a second course of Vira A and, in another one, 65 months after stopping treatment; and one patient seroconverted during interferon-alpha 2b therapy.

We can argue in some instances that late HBeAg to anti-HBeAb seroconversion may not be the direct effect of the antiviral agent, but rather the natural outcome and/or the consequence of stopping CS, which has been demonstrated to delay HBeAg to anti-HBeAb seroconversion but whose withdrawal triggers it. These results are much better than those obtained with CS, which rarely, if ever, allow seroconversion but, on the contrary, favor high levels of virus replication, thereby favoring the development of chronic liver disease. The combination of Vira A and PE was well tolerated by the patients and only

minor side-effects were observed. Vira A dose supplementation is not recommended (15), because the short duration of PE means that less than 8% of the daily dose is eliminated. No definitive withdrawal of treatment was necessitated by side-effects.

At present, more powerful antiviral agents, such as interferon-alpha and lamivudine, are available and Vira A is no longer prescribed. Adopting the same strategy as that devised for Vira A, we have successfully treated ten patients: six who have seroconverted from HBeAg to anti-HBeAb and four who have seroconverted from HBsAg to anti-HBsAb (16). Treatment was well tolerated. We recently conducted a prospective trial combining lamivudine and PE (Treatment of hepatitis B virus-related polyarteritis nodosa with lamivudine and plasma exchanges: a prospective, multicenter, pilot trial in 10 patients, American College of Rheumatology, San Francisco 10–14 November, 2001). The results showed that nine out of 10 patients recovered and that six out of 10 underwent HBeAg to anti-HBeAb seroconversion. The regimen was well tolerated with few side-effects. Nevertheless, because of the rarity of the disease and the dramatic improvement obtained with this innovative antiviral strategy, we did not propose a randomized trial comparing the antiviral and PE strategy to more conventional therapy combining CS and cytotoxic drugs.

Treatment strategies

Twenty-two years of therapeutic trials using PAN and CSS enable us to propose the following strategies according to disease characteristics.

For polyarteritis nodosa without Hepatitis B virus and Churg–Strauss syndrome

Prednisone in combination with CYC improves disease control despite infectious side-effects, which can be limited by better dose adaptation as a function of neutrophil and lymphocyte counts. We can expect that other modalities of treatment with CYC could favor better clinical results and a lower rate of infectious side-effects. We have also demonstrated that pulses and oral CYC have comparable efficacies. No long-term side-effects were observed and no leukemia or lymphoma was attributed to the CYC treatment during long-term follow-up. For PAN, 12 months of CYC suffices. It is also possible that CYC could be more effective in some PAN subgroups, for instance those with clinical symptoms of poor prognosis. We are presently attempting to optimize CYC prescription in PAN and CSS, and thereby improve prognosis.

For HBV-related polyarteritis nodosa

The first-line treatment should be the combination of antiviral agents and PE. This regimen is effective and cures a majority of patients within 2–3 months. Half of them seroconverted and are no longer exposed to future complications of HBV replication, such as liver cirrhosis. Unfortunately, it is not possible to clear the virus in every patient, as was observed in chronic hepatitis. The duration of the infection before the diagnosis, the lapse of time before treatment initiation and previous immunosuppression contribute to a poor seroconversion rate.

The role of PE in the treatment of systemic necrotizing angiitis

Plasma exchange is obviously useful in HBV-related PAN. Side-effects of PE are minor and transient. No patient developed long-term side-effects of PE, such as HBV or hepatitis C virus (HCV) infections because albumin was systematically used as the replacement fluid during PE. For PAN not related to HBV and CSS, there is presently no argument to support the systematic prescription of PE at the time of diagnosis. Plasma exchange could be indicated in subgroups of patients, more to control disease progression than to improve survival. Plasma exchange might also facilitate recovery from some symptoms and limit the intensity of sequelae but these have not yet been scientifically demonstrated in PAN and CSS.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES-ASSOCIATED VASCULITIDES

Some systemic necrotizing vasculitides affecting small-sized vessels are associated with antineutrophil cytoplasmic antibodies (ANCA). This group of diseases includes: pauci-immune glomerulonephritis (GN), Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and CSS. Classification of systemic vasculitides has been largely influenced by the new pathogenic concepts and a better understanding of histology. It also explains that therapeutic trials designed prior to these clarifications included diseases that are now considered to be very different (i.e. PAN, MPA and CSS).

Pauci-immune rapidly progressive glomerulonephritis

Many patients presenting with crescentic GN have WG, MPA or kidney-limited pauci-immune GN. Several randomized trials tested the indications of PE in patients with pauci-immune rapidly progressive glomerulonephritis (RPGN.) Glöckner et al. (17)

then Cole et al. (18) organized prospective trials in which patients were randomly assigned to receive immunosuppressants (corticosteroids (CS), CYC, azathioprine) with or without PE. Those studies did not demonstrate any advantage of PE adjunction. Conversely, Pusey et al. (19) provided evidence of a benefit in a subgroup of patients who presented with dialysis-dependent diseases. Patients received CS and immunosuppressive agents, and were randomized to undergo PE, at least three to four sessions a week for a total of 5 weeks. Ten of the 11 dialyzed patients undergoing PE recovered sufficient renal function to stop dialysis versus three of eight patients in the other group. Rifle and Dechelette (20) obtained comparable results. The best results were achieved in the subgroup of patients with severe renal insufficiency. However, survival was not prolonged for any study patients. These contradictory results are in part the consequence of the small number of patients included in each trial. The European Vasculitis (EUVAS) Group has designed a prospective large-scale study (presented at the World Apheresis Association Congress, Paris, 6–10 September 2002) to compare PE to pulse methylprednisolone in patients with ANCA-associated vasculitides presenting renal insufficiency characterized by creatininemia $\geqslant$ 500 µmol/L. Both groups of patients received CS and CYC. One hundred and fifty patients have been included and the preliminary results for 123 patients indicate that PE are superior to methylprednisolone to prevent dialysis at 3 months (15 vs. 36%). No difference in mortality has been observed.

Goodpasture's syndrome

Antiglomerular basement membrane (GBM) Ab disease presents as RPGN with or without alveolar hemorrhage. This disease is now considered to be a vasculitis affecting small-sized vessels. Rapidly progressive crescentic GN is characterized by IgG and C3 deposits. Without treatment, the majority of patients die quickly. Under a combination of CS and cytotoxic drugs, prognosis remained poor. The adjunction of PE proved beneficial and study results (21,22) demonstrated that PE was able to lower anti-GBM Ab titers and creatininemia, and fewer patients progressed to renal failure. In a randomized trial, Johnson et al. (22) demonstrated that patients undergoing PE had 50% lower creatininemia levels.

In light of these findings, we conclude that PE should be added to immunosuppressants to treat Goodpasture's syndrome. For the most severe cases, when creatininemia is greater than 600 µmol/L, the effect of PE on renal function has not been demonstrated, but they remain a major component of the treatment of alveolar hemorrhage. Daily exchanges of 60 mL/kg of body weight with 4% albumin replacement fluid are recommended for 14 days.

Wegener's granulomatosis and microscopic polyangiitis

Except for patients with severe GN, PE is not proposed as the first-line treatment of WG and MPA. Corticosteroids and CYC are uniformly given. Only anecdotal publications have shown PE to be beneficial, but infectious side-effects counterbalance these potential advantages.

OTHER VASCULITIDES

IgA nephropathy

IgA nephropathy can be observed in Henoch–Schönlein purpura (HSP) and can be severe. Plasma exchange has been recommended as adjunctive treatment to immunosuppressive drugs and CS in patients with severe GN associated with IgA deposits. IgA nephropathy is the most common GN worldwide. Only in a minority of patients does HSP progress to renal failure. Henoch–Schönlein purpura (23) and Berger's disease present the same histological aspects. Treatment of IgA nephropathy is not codified and different therapeutic approaches have been attempted.

Plasma exchange has been tested in individual patients or small series (24,25). Nicholls et al. (26) achieved significantly slower impairment of renal function in 13 patients with progressive renal deterioration. The benefit of PE has never been demonstrated in a large series and prospective studies are needed.

Cryoglobulinemia

Plasma exchange is frequently prescribed in the therapeutic strategy for cryoglobulinemia. In type I symptomatic patients, PE is combined with cytotoxic agents. In this indication, PE should not be used alone as a rebound phenomenon may occur.

Type II and III cryoglobulinemias are, in most cases, the consequence of HCV (27,28), which is detected in at least 80% of the patients. Hepatitis C virus-related cryoglobulinemia is a vasculitis affecting small-sized vessels. Vasculitis is the consequence of immune-complex deposition. In addition to cryoglobulins, rheumatoid factor is present and the C4 fraction is low. Type II cryoglobulinemia has a monoclonal component, usually IgM kappa, while type III has polyclonal Ig (29). Systematic investigations in patients with HCV infection show that half of them have cryoglobulinemia but that it is asymptom-

atic. Cryoglobulinemia requiring therapeutic intervention is rare. Plasma exchange is indicated for severe GN, mononeuritis multiplex, chronic leg ulcers or other vascular manifestations (30). They are effective in combination with interferon-alpha. We recommend three sessions a week for 3 weeks followed by two sessions a week for 2 or 3 weeks and then 1 session a week over a prolonged period (30,31). Complete virus eradication is obtained only in a minority of patients and HCV-related cryoglobulinemia is a chronic disease requiring a chronic treatment (32). Treatment duration cannot be established a priori because of persistent disease and frequent relapses. In this indication, long-term PE is necessary to control the clinical manifestations of cryoglobulinemia (30,33). Plasma exchange should be combined with interferon-alpha and with CS in refractory cases. We do not recommend the systematic prescription of CS as the first-line treatment because it stimulates virus replication and, consequently, can jeopardize clinical evolution. Hepatitis C virus-related cryoglobulinemia is a major concern for clinicians, especially in countries around the Mediterranean Sea where its prevalence is high. Therapeutic trials have tested antiviral agents but without success in most cases. The indications of PE, which are obviously effective in subgroups of patients, need to be prospectively evaluated.

HIV-related vasculitis

Human immunodeficiency virus (HIV) can be, but rarely is, responsible for systemic vasculitides. Necrotizing or non-necrotizing vasculitides may develop and their severity requires intensive treatment intended to attenuate the vasculitis without impairing the patient's general condition. Corticosteroids and immunosuppressants are contraindicated because they stimulate virus replication and can favor the occurrence of opportunistic infections. Plasma exchange has been used successfully and we have designed a therapeutic approach comparable to that applied to other virus-associated vasculitides. The combination of PE and antiretroviral agents, mainly zidovudine, has been given to patients. In all cases, the vasculitis was attenuated without concomitant deterioration of the acquired immunodeficiency syndrome (AIDS), in contrast to what has been observed with CS.

The pathogenesis of HIV-related vasculitis is not fully understood. HIV antigens have been detected in muscle and nerve perivascular cells in patients with vasculitis. HIV has selective tropism for the cell-surface CD4 glycoprotein. This glycoprotein is expressed on T lymphocytes and cells of the monocyte/macrophage lineage, which are therefore potential targets for infection by HIV. Monocytes/macrophages are also an important reservoir for HIV. In vitro, these cells have been shown to be permissive for HIV replication but in vivo HIV replication is rarely observed in them (34). Why perivascular cells, which constitute reservoirs for latent HIV, become local sources of HIV remains to be elucidated and the role of viral coinfections, which may enhance HIV replication, cannot be ruled out. Cytokines released by immunocompetent cells are known to be potent triggers of HIV replication in macrophages. Their secretion can be induced by infectious agents and immune complexes. It is possible that complex interactions among immune complexes (either deposited from the bloodstream or formed in situ), the cytokine network and the perivascular cells result in the local release of increasing amounts of antigens and cytokines, which, in turn, initiate and amplify the vascular inflammatory process. Plasma exchange could interfere with humoral and cellular factors responsible for vasculitis and thereby induce clinical improvement. We have shown in eight patients that PE in combination with zidovudine was able to successfully treat the vasculitis, without adversely affecting the AIDS course (35).

Vasculitis of autoimmune diseases

Vasculitis can be observed in several autoimmune diseases such as: systemic lupus erythematosus, Sjögren's syndrome, and scleroderma. Usually, treatment is based on the combination of CS and immunosuppressants. Plasma exchange can help control the disease and attenuate the vasculitis but no study has been performed to evaluate precisely the indications of PE.

CONCLUSION

Plasma exchange treatments have been widely used over the past few decades, and prospective trials and new regimens have more firmly established their indications and limited their number. Nevertheless, PE still has a large role, in most cases in conjunction with other treatments. New treatments, like high-dose intravenous immunoglobulins (IVIg) or antitumor necrosis factor-alpha (TNFα) Ab, have often overtaken PE, but indications of PE and other immunomodulating agents are not strictly superimposable. At present, no known criteria can predict who will respond and who will not. Further studies are now necessary to determine the respective indications of the different immunomodulating therapies now available.

REFERENCES

1. Cohen RD, Conn DL, Ilstrup DM. Clinical features, prognosis, and response to treatment in polyarteritis. *Mayo Clin Proc* 1980;55:146–55.
2. Frohnert P, Sheps S. Long term follow-up study of polyarteritis nodosa. *Am J Med* 1967;43:8–14.
3. Leib E, Restivo C, Paulus H. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. *Am J Med* 1979;67:941–7.
4. Fauci A, Doppman J, Wolff S. Cyclophosphamide-induced remission in advanced polyarteritis nodosa. *Am J Med* 1978;64:890–4.
5. Lockwood C, Rees A, Pinching A. Plasma exchanges and immunosuppression in the treatment of fulminating immune complex crescentic nephritis. *Lancet* 1977;1:63–7.
6. Blétry O, Bussel A, Badelon I et al. Intérêt des échanges plasmatiques au cours des angéites nécrosantes. Onze cas. *Nouv Presse Méd* 1982;11:2827–31.
7. Chalopin J, Rifle G, Turc J, Cortet P, Severac M. Immunological findings during successful treatment of HBs Age-associated polyarteritis nodosa by plasmapheresis alone. *Br Med J* 1980;1:368.
8. Guillevin L, Tanter Y, Blétry O et al. Treatment of severe polyarteritis nodosa with plasma exchange. *Prog Artif Organs* 1983: 723–6.
9. Lockwood C, Worledge S, Nicholas A, Cotton C, Peters D. Reversal of impaired splenic function in patients with nephritis or vaculitis (or both) by plasma exchange. *N Engl J Med* 1979;300:524–30.
10. Guillevin L, Jarrousse B, Lok C et al. Longterm followup after treatment of polyarteritis nodosa and Churg–Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa. *J Rheumatol* 1991;18:567–74.
11. Guillevin L, Fain O, Lhote F et al. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg–Strauss syndrome. A prospective, randomized trial in 78 patients. *Arthritis Rheum* 1992;35:208–15.
12. Guillevin L, Lhote F, Gayraud M et al. Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75:17–28.
13. Guillevin L, Lhote F, Jarrousse B et al. Polyarteritis nodosa related to hepatitis B virus. A retrospective study of 66 patients. *Ann Méd Interne (Paris)* 1992;143:63–74.
14. Guillevin L, Lhote F, Léon A, Fauvelle F, Vivitski L, Trépo C. Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges. A prospective trial in 33 patients. *J Rheumatol* 1993;20:289–98.
15. Fauvelle F, Léon A, Nicolas P, Tod M, Guillevin L, Petitjean O. Pharmacokinetics of vidarabine in the treatment of polyarteritis nodosa. *Fundam Clin Pharmacol* 1992;6:11–15.
16. Guillevin L, Lhote F, Sauvaget F et al. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. *Ann Rheum Dis* 1994;53: 334–7.
17. Glockner WM, Sieberth HG, Wichmann HE et al. Plasma exchange and immunosuppression in rapidly progressive glomerulonephritis: a controlled, multi-center study. *Clin Nephrol* 1988;29:1–8.
18. Cole E, Cattran D, Magil A et al. A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group. *Am J Kidney Dis* 1992;20:261–9.
19. Pusey C, Rees A, Evans DJ, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int* 1991;40:757–63.
20. Rifle G, Dechelette E. Treatment of rapidly progressive glomerulonephritis by plasma exchange and methylprednisolone pulses. A prospective randomized trial of cyclophosphamide. Interim analysis. The French Cooperative Group. *Prog Clin Biol Res* 1990;337:263–7.
21. Simpson IJ, Doak PB, Williams LC et al. Plasma exchange in Goodpasture's syndrome. *Am J Nephrol* 1982;2:301–11.
22. Johnson J, Moore J, Austin HA Jr, Balow JF, Antonovych T, Wilson C. Therapy of anti-glomerular basement membrane antibody disease. Analysis of prognostic significance of clinical, pathologic and treatment factors. *Medicine (Baltimore)* 1985;64:219–27.
23. Duquesnoy B. Henoch–Schönlein purpura. *Baillieres Clin Rheumatol* 1991;5:253–61.
24. Coppo R, Basolo B, Giachino O et al. Plasmapheresis in a patient with rapidly progressive idiopathic IgA nephropathy. removal of IgA-containing circulating immune complexes and clinical recovery. *Nephron* 1985;40:488–90.
25. Coppo R, Basolo B, Roccatello D, Piccoli G. Plasma exchange in primary IgA nephropathy and Henoch–Schönlein purpura. Plasma. *Ther Transfus Technol* 1985;6:705–23.
26. Nicholls K, Becker G, Walker R, Wright C, Kincaid-Smith P. Plasma exchange in progressive IgA nephropathy. *J Clin Apheresis* 1990;5:128–32.
27. Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. *N Engl J Med* 1992;327:1490–5.
28. Ferri C, Marzo E, Longbardo G. Interferon-alpha in mixed cryoglobulinemia patients. A randomized crossover-controlled trial. *Blood* 1993;81:1132–6.
29. Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins: a report of 86 cases. *Am J Med* 1974;57:775–88.
30. Rieu V, Cohen P, Andre MH et al. Characteristics and outcome of 49 patients with symptomatic cryoglobulinaemia. *Rheumatology (Oxford)* 2002;41:290–300.
31. Cohen P, Nguyen QT, Deny P et al. Treatment of mixed cryoglobulinemia with recombinant interferon alpha and adjuvant therapies. A prospective study on 20 patients. *Ann Méd Interne (Paris)* 1996;147:81–6.
32. Cacoub P, Maisonobe T, Thibault V et al. Systemic vasculitis in patients with hepatitis C. *J Rheumatol* 2001;28:109–18.
33. Frankel A, Singer D, Wienearls C, Evans D, Rees A, Pusey C. Type II essential mixed cryoglobulinemia: presentation, treatment and outcome in 13 patients. *Q J Med* 1992;82:101–24.
34. Gherardi R, Lebargy F, Gaulard P, Mhiri C, Bernaudin J, Gray F. Necrotizing vasculitis and HIV replication in peripheral nerves. *N Engl J Med* 1989;321:685–6.
35. Gisselbrecht M, Cohen P, Lortholary O et al. Human immunodeficiency virus-related vasculitis. Clinical presentation of and therapeutic approach to eight cases. *Ann Méd Interne (Paris)* 1998;149:398–405.