Role of intravenous immunoglobulin preparations (IVIG) in therapy of autoimmune diseases

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Abstract

Indications for application of high doses of intravenous immunoglobulin preparations (intravenous immunoglobulins – IVIG) have been significantly broadened in the recent decade. Results of the recent controlled clinical studies have accentuated a particular therapeutic value of IVIG in Kawasaki syndrome. At present, the treatment of choice for acute Kawasaki syndrome is a single dose of IVIG, at 2 gm/kg administered over 10–12 hours, in combination with acetylsalicylic acid. Literature of last years contains reports of variable effectiveness of IVIG in other autoimmune diseases, like anti-phospholipid syndrome, severe forms of thrombocytopenia in the course of systemic lupus erythematosus, some other severe forms of lupus with multiorgan manifestation, dermatomyositis, polymyositis, juvenile dermatomyositis and inclusion body myositis.

Attempts were made to administer IVIG in the course of lupus nephritis, systemic vasculitis and in the severe form of systemic juvenile arthritis. On the other hand, no favorable effects of IVIG could be demonstrated in rheumatoid arthritis.

Key words: *intravenous immunoglobulins, Kawasaki syndrome, anti-phospholipid syndrome, anti-cardiolipin antibodies, vasculitis*

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Indications for application of high doses of intravenous immunoglobulin preparations (intravenous immunoglobulins – IVIG) have been significantly broadened in the recent decade. Results of the recent controlled clinical studies have accentuated a particular therapeutic value of IVIG in Kawasaki syndrome [1, 2]. Literature of last years contains reports of variable effectiveness of IVIG in other autoimmune diseases, like:

- severe forms of thrombocytopenia in the course of systemic lupus erythematosus,
- anti-phospholipid syndrome,
- severe forms of lupus with multiorgan manifestation,
- dermatomyositis and polymyositis,
- juvenile dermatomyositis,
- inclusion body myositis.

Attempts were made to administer IVIG in the course of lupus nephritis, systemic vasculitis [3] (polyarteritis nodosa, Wegener's granulomatosis and other forms of *vasculitis*) and in the severe form of systemic juvenile arthritis. On the other hand, no favorable effects of IVIG could be demonstrated in rheumatoid arthritis.

Kawasaki syndrome (Ks)

Ks used to be defined as acute vasculitis in children. Most frequently it develops at the age of 6 to 24 months. The disease affects arteries of small and medium caliber. Diagnostic criteria of Kawasaki syndrome include: fever persisting 5 days or more, exhibiting no other etiology, plus presence of at least four of the following five criteria:

1) Nonexudative congestion of eyeball conjunctivae (develops in 90% patients).
2) Lesions in pharynx and oral cavity, such as reddening and chapping of lips, "strawberry tongue" or diffuse injection of pharyngeal mucosa (develop in almost every typical case).
3. Lesions on lower extremities, including exanthema on palms or soles, edema on hands and feet, and desquamation on fingertips.

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4. Polymorphic exanthema (in most of the patients).
5. Acute, nonpurulent cervical lymphadenopathy (appears in 50 to 75% patients).

Occasionally Ks takes an untypical course and, in such cases, the diagnosis can be established by less than four criteria if coronary artery aneurysms are demonstrated by cardiac ultrasonography or coronary angiography. Ks should be suspected in any child with protracted febrile conditions. The clinically most significant symptoms in the course of Ks are heart lesions. Within a week from the beginning of the disease myocarditis may be detected with the resulting exudate although the latter may exhibit a trend for spontaneous disappearance. Abnormalities of coronary vessels develop in approximately 25% patients which were not treated with IVIG.

Therapy of Ks includes aspirin. On the other hand, application of corticoids is not recommended due to their unfavorable effects on coronary vessels.

Beginning at early 1980s, large doses of intravenous immunoglobulins were introduced to treatment of Ks which brought about a definite progress in treatment of the disease and the respective prognosis.

If the diagnosis has been established in the first 10 days of the disease or if clinical signs/symptoms as well as exponents of the acute inflammatory condition persist, the treatment of choice of acute Ks is administration of a single IVIG infusion of 2 g/kg body weight. The infusion is administered for the period of 10 to 12 h, together with aspirin (ASA) at the dose of 80–100 mg/kg body weight/day in four divided doses till the 14th day providing that the patients remains afebrile. In most children, fever disappears within few hours after IVIG. This way of treatment is particularly advantageous also due to decreased frequency of lesions in coronary vessels and due to less frequent giant aneurysms, representing the most serious complications of the lesions [4]. Thirty percent of giant aneurysms lead to occlusion of the lumen in coronary vessels in approximately 32 months, which may precipitate sudden death in the patients. The disturbed function and contractility of the left ventricle have been found to disappear more rapidly in patients treated with IVIG + ASA than in patients treated with ASA only [5]. Administration of IVIG in the first 10–12 days of the disease prevents formation of aneurysms. Within 5–9 days after administration of IVIG control ultrasonographic examination of the heart should be performed. If no lesions to coronary vessels are seen within 14 days after the treatment, basically no risk exists of later development of aneurysms.

Administration of IVIG is followed by a rapid decrease in acute phase reactants. In patients who despite IVIG treatment develop lesions in coronary vessels, mononuclear leucocytes secrete augmented amounts of interleukin-1 (IL-1). This induces cytokine-dependent activation of endothelium. On the other hand, in patients with a favorable reaction to IVIG treatment secretion of IL-1 decreases to normal values. This indicates that IVIG alleviates Ks by decreasing cytokine-dependent activation of endothelium. Moreover, antibodies contained in IVIG block superantigen-mediated activation of lymphocytes T [6], which is resistant to corticoids. At present, administration of a single dose of IVIG is thought to be associated with less frequent pathology of coronary vessels, accelerated disappearance of fever and laboratory exponents of inflammation as compared to administration of few infusions (of the soma total dose). A single infusion decreases also duration of stay in a hospital and results in higher serum IgG levels [7]. In a small proportion of the patients elevated temperature persists for over 48 h or fever relapses after 24 h. In such situations repeated infusion of IVIG is recommended, at the dose of 2 g/kg since the persisting fever is accompanied by augmented levels of pro-inflammatory cytokines which in turn promotes pathology of coronary vessels [8].

Individual reports suggest that in cases when no reaction is noted to the repeated infusion of IVIG, administration of high corticosteroid dose (methylprednisolone at the dose of 30 mg/kg/day for the period of 1–3 days) may result in a beneficial effect [9]. In general, however, corticoids should not be given in Ks.

Anti-phospholipid syndrome

Diagnosing of anti-phospholipd syndrome (Aps) requires that at least one relevant clinical sign (episode of vascular thrombosis, complications of pregnancy) is detected and abnormal antibody titers are demonstrated (moderate or high titers of anti-cardiolipin antibodies [aCL] or positive lupus anticoagulant) noted at least on two occasions, spaced by at least 6 weeks.

Heparin and aspirin inhibit effects of Aps while administration of IVIG decrease levels and, probably, continuous production of anti-phospholipid antibodies (aPL).

Administration of IVIG is focused mainly on obstetric complications, particularly on recurrent abortions. Reports are also available on effects of IVIG on other clinical signs/symptoms of Aps, as listed in Table 1.

In the animal model of Aps, induced in mice, significantly less frequent fetal losses were noted following treatment with IVIG as compared to untreated mice [16]. In humans with Aps, IVIG was applied for the first time in 1988 [17], in a woman with nine abortions in anamnesis. Further attempts aimed at determining the most optimal dosing schedule. IVIG was administered with success in 14 women with diagnosis of Aps and recurrent abortions in anamnesis, given as follows: 500 mg/kg body weight/day for two consecutive days, beginning from 5th week of pregnancy and ending at 33rd week of pregnancy, every 4 weeks [18]. All the patients delivered healthy babies of a normal birth weight. Only one patient developed a complication in the form of arterial hypertension.

Other investigators [19] administered IVIG in the course of 19 pregnancies among 15 women with diagnosis of Aps, at the dose of 400 mg/kg/day for 5 consecutive days every

Table 1. Reports on treatment of anti-phospholipid syndrome

Author	Clinical sign	Remarks
Sturfelt et al., 1990 [10]	Thrombocytopenia	Favorable effect of IVIG after failure of steroid and cytostatic therapy
Cohen, Lui, 1992 [11]	Hemolytic anemia, thrombocytopenia, thrombosis, pulmonary hemorrhages	Steroids, plasma exchange, IVIG and cyclophosphamide did not control the signs, rapid improvement of anemia and thrombocytopenia following low doses of aspirin
Takagi, Shigekyio, 1993 [12]	Bleeding due to thrombocytopenia	IVIG therapy decreased activity of lupus anticoagulant and augmented levels of blood platelets
Arnout et al., 1994 [13]	Habitual abortions, thrombocytopenia	IVIG induced preterm delivery of a healthy child and increased level of blood platelets
Vandenberghe et al., 1996 [14]	Autoimmune hemolytic anemia	Few cycles of IVIG resulted in cessation of hemolysis
Vivaldi et al., 1997 [15]	Acquired hypoproteinemia	IVIG and steroids corrected prothrombin time

month or at the dose of 1000 mg/kg/day for two consecutive days every month. The cycles were started in the first trimester or at early stage of the second trimester of pregnancy. Sixteen out of those 19 pregnancies (84%) were favorably terminated. In fifteen of those 18 gravidas subcutaneous heparin and low doses of aspirin were given in parallel which makes interpretation of the results difficult.

In the other therapeutic trial IVIG [20] was given to 38 women with diagnosed Aps and three consecutive abortions in the first trimester, according to the following schedule: IVIG 300 mg/kg every three weeks from the moment of diagnosing pregnancy to 16^{th}–17^{th} week of pregnancy. In 89.4% (34 out of 38 cases) pregnancy persisted beyond the first trimester and 81.4% of the women (31 out of 38) delivered newborns at term.

Level of anti-cardiolipin antibodies (ACL) decreases immediately after the infusion but returns to the elevated level two weeks after terminating the infusions [21].

At present, three potential mechanisms are recognized which affect ACL level:

1. Anti-idiotypic antibodies may be present in IVIG preparations. They bind autoantibodies forming idiotype-anti-idiotype complexes which neutralize activity of autoantibodies.
2. Anti-idiotypic antibodies may inhibit receptors on lymphocytes B and may decrease production of autoantibodies.
3. Anti-idiotypic antibodies may bind receptors on T lymphocytes which leads to inhibition of lymphokine synthesis and lowered activation of autoantibody production by lymphocytes B [22].

Administration of IVIG is seldom accompanied by severe side effects. In individual cases only a feeling of a burden or pain in the chest was experienced, nausea or weakness. If vasomotoric reactions appear the rate of infusion should be reduced and in more severe cases administration of acetaminophen, antihistamines and corticosteroids may be recommended. Patients with IgA deficiency, who may be expected to develop anaphylactic reactions, are seldom encountered. Sporadically, hemolysis accompanies IVIG administration, which may be linked to anti-erythrocyte alloantibody content in IVIG preparation. In individual cases IVIG administration was observed to be followed by thrombosis and aseptic meningitis.

IVIG therapy of Aps is linked to very high costs. The IVIG dose of 400 mg/kg/day for 5 days in a week may be associated with monthly costs of treatment of 4000 USD to 5000 USD, and it is necessary to administer an average of 6–7 cycles [21]. Nevertheless, such complications as retarded intrauterine development, pre-eclampsia, preterm delivery, placental abnormalities develop much less frequently in patients treated with IVIG, which decreases frequencies of long term hospital treatment.

Attempts have also been made to use IVIG in women with infertility and presence of anti-phospholipid antibodies in whom earlier artificial fertilization was applied with no success. IVIG therapy was applied in 89 infertile women who earlier experienced at least four ineffective artificial fertilization rounds [23]. The group included 52 women with anti-phospholipid antibodies (Apa) and 37 women who did not carry such antibodies. Each of them received 81 mg aspirin, 10 000 U heparin and a single infusion of 20 g IVIG 3–10 days before fertilization. Success of the overcoming the infertility was obtained in 42% (22 out of 52) women with Apa as compared to 19% (7 out of 37) women without such antibodies ($p=0.02$).

Thrombosis represents the most significant clinical problem in Aps and administration of aspirin and heparin decreases frequency of the complication. However, Apa affect other mechanisms than the clotting system. They affect pulsatory pattern of secretion of human chorionic gonadotropin by the placenta, which unfavorably affects the fetus. In such situations, anti-thrombotic drugs are insignificant while IVIG neutralize the antibodies and effectively promote fetal well-being.

Systemic lupus erythematosus

In severe cases of lupus, resistant to earlier therapeutic attempts and when life is endangered by multiorgan complications, particularly in cases of severe thrombocytopenia IVIG infusions have been attempted with variable effects [24]. Relatively favorable effects of IVIG therapy were described using the dose of 400 mg/kg for 5 consecutive days in 9 patients with SLE, uremia and nephrotic syndrome, who failed to benefit from pulse treatment with methylprednisolone and cyclophosphamide [25]. In all 9 patients a marked decrease was observed in creatinine level, proteinuria and anti-DNA antibody titers. In 7 patients who were re-tested by biopsy 2 months after the treatment an extensive decrease was observed in amounts of deposited immune complexes.

IVIG treatment of 20 patients with severe form of lupus resulted in advantageous effects of the treatment in 17/20 patients (85%) [26]. The patients were treated with 2 g/kg IVIG every month for a period of 5 days. Every patient received 1 to 8 cycles of the treatment. Estimation of SS-A and SS-B antibodies and of complement levels allowed to distinguish patients with the potential for favorable response to the treatment. The patients could be distinguished due to significant abnormalities in tests which became normalized following the treatment. IVIG therapy most effectively alleviated lupus signs such as arthritis, fever, thrombocytopenia and neuropsychiatric signs/symptoms.

Dermatomyositis and polymyositis (DM/PM)

A double blind trial of administering IVIG vs placebo was performed on 15 adult DM patients, resistant to treatment (>4 months of treatment with high doses of steroids or of other immunosuppressive drugs). IVIG was applied at 2 g/kg body weight on three occasions spaced by one month with the potential for cross alteration of the therapy following 3 months [27]. Eight patients who received IVIG demonstrated a significant improvement while no such effect could be noted in 7 patients receiving placebo. Out of the total of 12 patients who were treated with IVIG in the sample, in 9 an almost complete improvement, in 2 mild improvement was noted and in only one patient no effect of the treatment could be detected. However, the beneficial effects persisted for 6 weeks only suggesting need for a more protracted treatment.

In controlled studies the highest efficacy of the treatment was observed in DM, in which improvement included both muscle strength and skin condition. In inclusion body myositis improvement was reached in some patients but analysis of the entire group failed to disclose significant benefits. In polymyositis results of studies documented improved muscle strength but the result requires confirmation in controlled studies [28]. Certain hints as to expected efficiency of treatment could be obtained by monitoring of sIL-2R levels in serum. Decrease in the parameter is observed in patients who respond well to this type of treatment. On the other hand, CPK level remains prognostically useless as it fails to correlate with activity of disease in the cases [29].

Juvenile dermatomyositis [JDM]

In uncontrolled studies [30], a sample of 11 patients (resistant to corticosteroid treatment) demonstrated improvement in all the children, with augmented muscle strength and a decreased level of creatine kinase (CPK). In all the patients prednisone could be discontinued or its doses reduced. In children with IgA deficiency, IgA-free preparations should be used due to the risk of anaphylactic reactions. Occasionally, the children may develop liquid overload, allergic reactions or aseptic meningitis.

Other authors described 18 children with JDM who did not react to steroids and for this reason were treated with IVIG. Clinical improvement and potential for reduction of steroid dose was reached in 12 patients [31].

Juvenile chronic arthritis (JCA)

Double blind multicenter studies failed to confirm full effectiveness of IVIG, particularly in the systemic form of the disease, although the involved number of patients was low [32].

Diffuse scleroderma

Recently the attempt was described of IVIG therapy in 3 patients with rapidly progressing scleroderma [33]. In all the patients improved condition of the skin was observed. They received (2 of 3 patients) IVIG cycles (2 g/kg body weight) spaced by one month for the period of 6 months.

Vasculitis

The rationale for treating Wegener's granulomatosis with IVIG was demonstration that ANCA (anti-cytoplasmic antibodies, pathognomic for the disease) reacted with anti-idiotypic antibodies contained in immunoglobulin preparations. Two open clinical tests were conducted, employing 400 mg/kg/day for 5 days. The first group included 14 patients with systemic vasculitis and ANCA presence [3]. Clinical improvement was reached in 9 patients but upon extended preparations in three of the patients exacerbation developed. In other clinical studies on 13 patients with Wegener's granulomatosis no patient reached the complete remission and no improvement could be noted in ocular, pulmonary or renal signs/symptoms [34]. Repetitions of the therapeutic cycles were as inefficient as a single cycle of treatment.

However, results of a randomized, double blind clinical study with administration of a single IVIG cycle (at the total dose of 2 g/kg body weight) on a more numerous group of patients with systemic vasculitis (Wegener's granulomatosis and microscopic polyangitis) are more encouraging [35]. Clinical response, following obtaining a partial remission, was observed in 14 out of 17 patients but only in 6 out of 17 patients treated with placebo. The effect of treatment persisted for no longer than 3 months which would suggest the need for repeating IVIG infusions every 3 months to

support the remission and to reduce doses of applied corticosteroids and/or cytostatic drugs.

In children with vasculitis, resembling nodular vasculitis as a complication of chronic infection with parvovirus B19, administration of IVIG brought about a significant improvement [36]. This may point to certain disturbances of immune reactivity in the children upon contact with parvovirus B19.

References

1. Newburger JW, Takashi M, Burns JC, et al. (1986): The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 315: 341-7.
2. Leung DYM, Schlievert PM, Meissner HC (1998): The immunopathogenesis and management of Kawasaki syndrome. Arthritis Rheum 41: 1538-47.
3. Jayne DR, Lockwood CM (1993): Pooled intravenous immunoglobulin in the management of systemic vasculitis. Adv. Exper Med Biol 336: 469.
4. Rowley AH, Duffy CE, Shulman ST (1989): Prevention of giant coronary artery aneurysms in Kawasaki disease by intravenous gamma globulin therapy. J Pediatr 114: 1065-6.
5. Newburger JW, Sanders SP, Burns JC, et al. (1989): Left ventricular contractility and function in Kawasaki syndrome: effect of intravenous gamma-globulin. Circulation 79: 1237-46.
6. Takei S, Arora YK, Walker SM (1993): Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens. J Clin Invest 91: 602-7.
7. Newburger JW, Takayashi M, Beiser AS, et al. (1991): A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 324: 1633-9.
8. Koren G, Lavi S, Rose V, et al. (1986): Kawasaki disease: review of risk factors for coronary aneurysms. J Pediatr 108: 388-92.
9. Kato H, Koike S, Yokoyama T (1979): Kawasaki disease: effect of treatment on coronary artery involvement. Pediatrics 63: 175-9.
10. Sturfelt G, Mousa F, Jonsson H, et al. (1990): Recurrent cerebral onfarction and the antiphospholipid syndrome: effect of intravenous gammaglobulin in a patient with systemic lupus erythematosus. Ann Rheum Dis 49: 939-41.
11. Cohen MG, Lui SF (1992): Multiple complications of the antiphospholipid syndrome with apparent response to aspirin therapy. J Rheumatol 19: 803-6.
12. Takagi M, Shigekiyo T (1993): Gammaglobulin infusion therapy in a patient with antiphospholipid syndrome. Jpn J Clin Hematol 34: 496-8.
13. Arnout J, Spitz B, Wittevrongel C, et al. (1994): High-dose intravenous immunoglobulin treatment of pregnant patient with antiphospholipid syndrome: immunological changes associated with a successful outcome. Thromb Haemost 71: 741-7.
14. Vandenberghe P, Zachee P, Verstraete S, et al. (1996): Successful control of refractory and life-threatening autoimmune hemolytic anemia with intravenous immunoglobulins in man with the primary antiphospholipid syndrome. Ann Hematol 73: 253-6.
15. Vivaldi P, Rosetti G, Galli M, et al. (1997): Severe bleeding due to acquired hypoprothrombinemia-lupus anticoagulant syndrome. Case report and review of the literature. haematologica 82: 345-7.
16. Bakimer R, Guilburd B, Zurgil N, et al. (1993): The effect of intravenous γ-globulin on the induction of experimental antiphospholipid syndrome. Clin Immunol Immunopathol 69: 97-102.
17. Carreras LO, Perez GN, Vega HR, et al. (1988): Lupus anticoagulant and recurrent fetal loss: successful treatment with gammaglobulin. Lancet 2: 393-4.
18. Valensise H, Vaquero E, De Carolis C, et al. (1995): Normal fetal growth in women with antiphospholipid syndrome treated with high-dose intravenous immunoglobulin (IVIG). Prenatal Diag 15: 509-17.
19. Clark AL, Branch DW, Silver RM, et al. (1999): Pregnancy complicated by the antiphospholipid syndrome: outcomes with intravenous immunoglobulin therapy. Obstet Gynecol 93: 437-41.
20. Marzusch K, Dietl J, Klein R, et al. (1996): Recurrent first trimester spontaneous abortion associated with antiphospholipid antibodies: a pilot study of treatment with intravenous immunoglobulin. Acta Obstet Gynecol Scandinavica 75: 922-6.
21. Spinnato JA, Clark AL, Pierangeli SS, et al. (1995): Intravenous immunoglobulin therapy for the antiphospholipid syndrome in pregnancy. Am J Obstet Gynecol 172: 690-4.
22. Dwyer JM. Manipulating the immune system with immunoglobulin (1992): New Engl J Med 326: 106-7.
23. Sher G, Zouves C, Feiman M, et al. (1998): A rational basis for the use of combined heparin/aspirin and IVIG immunotherapy in the treatment of recurrent IVF failure associated with antiphospholipid antibodies. Am J Reprod Immunol 39: 391-4.
24. Sany J (1994): Intravenous immunoglobulin therapy for rheumatic diseases (review). Curr Opin Rheumatol 6: 305-10.
25. Lin CY, Hsu HC, Chaing H (1989): Improvement of histological and immunological change in steroid and immunosupressive drug-resistant lupus nephritis by high-dose intravenous gamma-globulin. Nephron 53: 303-10.
26. Levy Y, Sherer Y, Langevitz P, et al. (1999): A study of 20 SLE patients with intravenous immunoglobulin – clinical and serologic response. Lupus 8: 705-12.
27. Dalakas MC, et al. (1993): A controlled trial with high-dose intravenous immunoglobulins infusions as treatment for dermatomyositis. N Engl J Med 329: 1993-2000.
28. Dalakas MC (1998): Controlled studies with high-dose intravenous immunoglobulin in the treatment of dermatomyositis, inclusion body myositis, and polymyositis. Neurology 51 (6 Suppl 5): S37-45.
29. Gattfried I, Seeber A, Anegg B, et al. (2000): High dose intravenous immunoglobulin (IVIG) in dermatomyositis: clinical responses and effect on sIL-2R levels. Eur J Dermatol 10 (1): 29-35.
30. Barron KS, Sher MR, Silvermann ED (1992): Intravenous immunoglobulin therapy: magic or black magic. J Rheumatol 19 (suppl 33): 94-7.
31. Al-Mayouf SM, Laxer RM, Schneider R, et al. (2000): Intravenous immunoglobulin therapy for juvenile dermatomyositis: efficacy and safety. J Rheumatol 27 (10): 2498-503.
32. Uziel Y, Laxer RM, Schneider R, et al. (1996): Intravenous immunoglobulin therapy in systemic onset juvenile rheumatoid arthritis: A follow-up study. J Rheumatol 23: 910-18.
33. Levy Y, Sherer Y, Langevitz P, et al. (2000): Skin score decrease in systemic sclerosis patients treated with intravenous immunoglobulin – a preliminary report. Clin Rhematol 19 (3): 207-11.
34. Gross WL (1994): New developments in the treatment of sysytemic vasculitis. Curr Opin Rheumatol 6: 11-19.
35. Jayne DR, Chapel H, Adu D, Misbah S, O'Dohonghue D, Scott D, Lockwood CM (2000): Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. Q J Med 93: 433-9.
36. Finkel TH, Torok TJ, Ferguson PJ, et al. (1994): Chronic parvovirus B19 infection and systemic necrotizing vasculitis: Opportunistic infection or aetiological agent? Lancet 343: 1255-8.