Research article

Open Access

Intravenous immunoglobulin treatment of four patients with juvenile polyarticular arthritis associated with persistent parvovirus B19 infection and antiphospholipid antibodies

Hartwig W Lehmann[1], Annelie Plentz[2], Philipp von Landenberg[3], Esther Müller-Godeffroy[4] and Susanne Modrow[2]

[1]Rheumaklinik Bad Bramstedt, Bad Bramstedt, Germany
[2]Institute for Medical Microbiology, Universität Regensburg, Regensburg, Germany
[3]Department for Clinical Chemistry and Laboratory Medicine, Universität Mainz, Mainz, Germany
[4]Clinic of Pediatrics, Medizinische Universität Lübeck, Lübeck, Germany

Correspondence: Susanne Modrow (e-mail: susanne.modrow@klinik.uni-regensburg.de)

Received: 12 Jun 2003 Revisions requested: 26 Aug 2003 Revisions received: 29 Aug 2003 Accepted: 24 Sep 2003 Published: 10 Oct 2003

Arthritis Res Ther 2004, **6**:R1-R6 (DOI 10.1186/ar1011)

Abstract

Children with rheumatic oligoarthritis and polyarthritis frequently establish persistent parvovirus B19 infections that may be associated with the production of antiphospholipid antibodies (anti-PL IgG). In this study we analysed the influence of high-dose intravenous immunoglobulin (IVIG) therapy on virus load, on the level of anti-PL IgG and its potential capacity to improve the patients' clinical status. Four juvenile patients with long-lasting polyarticular rheumatic diseases and persistent parvovirus B19 infection, associated in three cases with the presence of antibodies against β_2-glycoprotein I (anti-β_2GPI IgG), were treated with two cycles of IVIG on five successive days (0.4 g/kg per day). Clinical parameters including scores of disease activity, virus load and anti-PL IgG levels were determined before, during and after treatment. Two patients showed a complete remission that has lasted 15 months. During that period they showed neither clinical nor laboratory signs of inflammation. Viral DNA was not detectable in serum, and a decrease in anti-β_2GPI IgG was observed. As assessed by the Childhood Health Assessment Questionnaire and the Health-related Quality of Life Questionnaire for Children, both patients were no longer restricted in their activities of daily living and no impact on the health-related quality of life was observed. In one patient the therapy failed: there was no improvement of symptoms and no decrease in virus load or inflammatory parameters. In the fourth patient, clinical and laboratory parameters did not improve despite a decrease in both viral load and anti-PL IgG. Our results show that the use of IVIG to treat parvovirus B19-triggered polyarticular rheumatic disease of childhood might offer an opportunity to improve this disabling condition.

Keywords: antiphospholipid antibodies, immunoglobulin therapy, juvenile arthritis, parvovirus B19, persistent infection

Introduction

Parvovirus B19 infection has been associated with a wide spectrum of diseases. Besides acute infection resulting in anaemia and erythema infectiosum (fifth disease), a rash illness of childhood, hydrops fetalis in pregnant women and acute symmetrical polyarthropathy in adults have been reported as clinical manifestations. Depending on the haematological status of the host, B19 infection can be associated with haematopoietic disorders such as anti-plastic crisis, thrombocytopenia and pancytopenia. Hepatitis, myocarditis, myositis, neurological disease and vasculitis can occur occasionally [1]. The relation of the infection to acute arthritis–arthralgias in children is well known. Some of the affected children develop chronic arthritis that is indistinguishable from juvenile idiopathic arthritis [2–5]. In these patients parvovirus B19 could

ANA = anti-nuclear antibodies; anti-PL IgG = antiphospholipid antibodies; β_2GPI = β_2-glycoprotein I; CK = creatine kinase; CRP = C-reactive protein; ENA = extractable nuclear antigens; ESR = erythrocyte sedimentation rate; IVIG = intravenous immunoglobulin; KINDL = Health-related Quality of Life Questionnaire for Children; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drugs; TCHA = triamcinolone hexaacetonid; VP1 = viral protein 1; VP2 = viral protein 2.

Table 1

Laboratory and clinical parameters of the patients before IVIG therapy

Patient	Disease (ILAR criteria)	Disease duration*	Joint erosion	Treatment	IgG antibodies		IgM antibodies		B19 DNA†		Anti-PL IgG		
					VP1/VP2	NS1	VP1/VP2	NS1	Serum	SF	Anti-CL	Anti-PS	Anti-β_2GPI
1	RF-positive polyarthritis	23	+	NSAID MTX TCHA Prednisolone (iv/oral)	++	–	++	–	10^3	10^2	–	–	++
2	Psoriatic arthritis	96	+	NSAID MTX TCHA	++	+	+	–	4×10^3	3×10^2	–	–	+
3	Psoriatic arthritis	48	–	NSAID MTX TCHA Prednisone	++	+	–	–	2×10^3	6×10^3	–	–	–
4	Reactive arthritis	125	–	NSAID Choroquine Prednisone Sulphasalazine	++	–	–	–	6×10^2	10^3	–	–	++

*Months before IVIG therapy. †Genome equivalents per ml of sample. Anti-β_2GPI, anti-β_2-glycoprotein I; anti-CL, anti-cardiolipin; anti-PL IgG; antiphospholipid antibodies; anti-PS, anti-phosphatidylserine; ILAR, International League of Associations for Rheumatology; iv, intravenous; IVIG, high-dose intravenous immunoglobulin; MTX, methotrexate; NS1, nonstructural protein 1; NSAID, nonsteroidal anti-inflammatory drugs; RF, rheumatoid factor; SF, synovial fluid; TCHA, intra-articularly injected crystalline glucosteroids; VP1, viral protein 1; VP2, viral protein 2.

frequently be detected in synovial fluid and serum samples. In some of the affected children the infection persisted over months and years. Furthermore we recently reported that in these children persistent parvovirus B19 infection was frequently associated with the presence of antiphospholipid antibodies (anti-PL IgG) [6].

During the past decade the treatment of various sequelae of chronic parvovirus B19 infection with high-dose intravenous immunoglobulin (IVIG) has emerged as a powerful tool to improve patient status or to cure the disease. In most instances, immunosuppressed patients or patients with haematopoietic disorders have been treated [1]. Solid organs (such as kidney) have also been shown to become infected by parvovirus B19 and to respond to immunoglobulin treatment [7]. Stahl and colleagues reported a marked improvement after IVIG treatment in two of three young patients with oligoarthritis and persistent infection with parvovirus B19 [8]. Here we show the results after treatment of four adolescents having different polyarticular rheumatic diseases triggered by parvovirus B19.

Materials and methods

Patients

For IVIG treatment we selected four patients with juvenile idiopathic arthritis that had lasted for between 23 and 125 months and persistent B19 infection. Patients were classified according to International League of Associations for Rheumatology criteria (Table 1).

Patient 1, a 12-year-old HLA-B27-negative girl, had rheumatoid-factor-positive polyarthritis (negative for antinuclear antibodies [ANA] and double-stranded DNA). Parvovirus B19-specific IgG and IgM antibodies were initially detected 4 months after the onset of symptoms and remained detectable during the whole observation time. At the beginning of the disease the cervical spine, one ankle and one metacarpophalangeal I joint were affected. Treatment was established with methotrexate (MTX) (subcutaneous, 12 mg/m^2 body surface per week) in combination with an intravenous prednisolone pulse. Despite a therapeutic regimen with combined applications of nonsteroidal anti-inflammatory drugs (NSAID), MTX and oral prednisolone, multiple relapses occurred in small and

large joints. First erosions (signal cysts) were seen. Multiple treatments with arthrocentesis and intra-articularly injected crystalline glucocorticosteroids (triamcinolone hexaacetonid; TCHA) were performed. B19 DNA was repeatedly amplified from synovial fluid and serum samples and anti-β_2GPI IgGs were detected (Table 1).

Patient 2, an HLA-B27-positive 17-year-old girl, had psoriatic arthritis with daktylitis and multiple psoriatic efflorescences. Disease started at the age of 9 years and activity was mild. After 7 years, mutilations of metatarsophalangeal V and erosions of metatarsophalangeal IV and metacarpophalangeal II joints were observed by X-ray. Frequent relapses occurred subsequently, requiring subcutaneous MTX (up to 20 mg/week), NSAID and multiple TCHA injections into small and large joints. X-ray examinations showed slow progression of the erosions. IgG against parvovirus B19 proteins VP1 and VP2, low titres of VP2-specific IgM and viral genomes were detected during the first serological screening performed at the age of 16 years. IgM antibodies and parvovirus DNA remained detectable, together with anti-β_2GPI IgG in subsequent serum and in all synovial fluid samples (Table 1).

Patient 3, an HLA-B27-negative 16-year-old boy, had psoriatic arthritis with psoriatic efflorescences at the scalp, starting with recurrent monoarthritis of the right knee at the age of 12 years. The patient was treated with low-dose prednisolone and repeated arthrocentesis of the knee. After a relapse affecting the right knee and the wrist, oral MTX was prescribed. During a relapse of the wrist and arthritis of the left elbow, both joints were treated with TCHA. Despite a weekly administration of 20 mg of subcutaneous MTX, he developed massive effusions of multiple large joints requiring TCHA. Parvovirus B19 DNA was detected in four different synovial fluid samples from the right knee, both hips and the left elbow, and in two serum samples obtained during the 6 months before the study (Table 1).

Patient 4, a 12-year-old girl, developed an effusion of the right knee at the age of 21 months. Because of the transitory presence of B19-specific IgM antibodies, parvovirus-associated reactive arthritis was diagnosed. Initially the patient was treated with NSAID, low-dose prednisone and chloroquine, which was subsequently replaced by sulphasalazine. Despite this treatment regimen the patient developed recurrent arthritis of both knees requiring multiple TCHA treatment, and arthroscopic synovectomy of the right knee was performed. After a long-lasting remission period NSAID treatment was stopped. Subsequently relapses of both knees occurred. At this time point, nearly 10 years after the initial detection of parvovirus B19-specific IgM, anti-β_2GPI IgG was detected and B19 DNA was amplified from serum. During a further flare (4 months before the study), B19 DNA was found in serum and in the synovial fluid of the left knee. The IVIG treatment was started after a relapse occurred in the left knee, both ankles and the calcaneo-cuboid and talo-navicular joints.

Treatment regimen and monitoring of the patients

IVIG (commercially available immunoglobulin preparations previously shown to contain large amounts of IgG against the viral capsid proteins VP1 and VP2 and to be free of contaminating B19 DNA; Varitect CP; Biotest, Dreieich, Germany) were administered at 0.4 g/kg body weight per day for 5 days. A second cycle of treatment was applied 4 weeks after the end of the first cycle. Patients were examined before each treatment cycle, 1 and 9 months after the end of the second cycle and subsequently at intervals of 3 months. Erythrocyte sedimentation rate (ESR), complete blood count, C-reactive protein (CRP), alkaline phosphatase, transaminases and γ-glutamyltransferase, creatine kinase, lactate dihydrokinase, protein electrophoresis, urinalysis, ANA, extractable nuclear antigens (ENA) and rheumatoid factor were determined. To exclude other infections with arthritis-associated infectious agents, various antibody titres were determined (for example *Borrelia*, *Yersinia*, *Campylobacter*, *Chlamydia*, *Salmonella* and streptolysin O). To estimate the clinical course, the number of affected joints was counted at each presentation. The affected joints were classified as active arthritis according to the American Rheumatism Association criteria.

Detection of B19-specific antibodies, immunocomplexes, genomes and anti-PL IgG

Patient samples were analysed for IgG and IgM against the structural and non-structural proteins of parvovirus B19 by Western blotting and ELISA assays (RecomBlot and RecomWell; Mikrogen GmbH, Munich, Germany). The total IgG content of these samples was determined by nephelometry. The amounts of immunocomplexed virus, of B19 DNA and of anti-PL IgG were determined as described [3,6].

Global assessment and disease impact on activities of daily living

In addition to the doctor's global assessment, both parent's global assessments were recorded on a visual analogue scale ranging from 0 (healthy) to 10 (severely affected). Restrictions in activities of daily living and the impact on the health-related quality of life were estimated by using the Childhood Health Assessment Questionnaire and the Health-related Quality of Life Questionnaire for Children (KINDL) as described [2]. Informed consent was obtained from the parents as well as from the patients.

Results

Apart from elevated inflammatory parameters, no gross abnormalities in the routine laboratory analysis were seen, except elevated concentrations of total IgG at the ends of both treatment cycles and 4 weeks after the second cycle in all patients. VP1-specific and VP2-specific reactions

Table 2

Laboratory and clinical parameters of the patients during IVIG therapy

Patient	Sample	ESR (mm/h)	WBC/ml	RBC/ml	Hb (g/dl)	CRP (mg/dl)	CK (U/l)	Arthritis (joints)	Total IgG (mg/dl)	B19 DNA		IgG anti-PL			VAS (doctor)	VAS (parents)
										Serum	SF	Anti-CL	Anti-PS	Anti-β_2GPI		
1	1	5	7.96	4.21	12.0	neg.	15	2	414	pos.	na	–	–	++	5	3
	2	nd	nd	nd	nd	nd	nd	nd	1832	neg.	na	–	–	+	nd	nd
	3	5	6.88	4.25	12.3	neg.	21	0	1430	pos.	na	–	–	–	1	1
	4	nd	nd	nd	nd	nd	nd	nd	2480	neg.	na	–	–	–	nd	nd
	5	9	9.58	4.36	12.3	neg.	16	0	1406	neg.	na	–	–	(+)	1	1
	6	9	7.0	4.4	12.2	neg.	17	0	nd	neg.	na	–	–	–	1	1
2	1	35	8.57	4.82	11.5	0.7	103	4	1450	neg.	na	–	–	+	4	4
	2	nd	nd	nd	nd	nd	nd	nd	3040	neg.	na	–	–	+	n.d	nd
	3	37	7.47	4.43	11.3	2.6	33	1	468	neg.	na	–	–	–	5	6
	3	nd	nd	nd	nd	nd	nd	nd	3680	neg.	na	+	++	++	nd	nd
	5	40	6.18	4.47	11.6	1.5	30	2	2020	pos.	na	–	–	–	4	6
	6	42	7.91	4.63	11.7	6.4	27	2	nd	neg.	na	–	–	–	5	7
3	1	15	6.33	4.84	13.5	0.5	20	0	864	pos.	na	–	–	–	5	5
	2	nd	nd	nd	nd	nd	nd	nd	3600	pos.	na	–	–	–	nd	nd
	3	12	6.96	4.61	13.1	0.7	25	0	1604	pos.	na	–	–	–	5	3
	4	nd	nd	nd	nd	nd	nd	nd	2420	pos.	pos.	–	++	+	nd	nd
	5	34	9.87	4.83	13.5	0.9	25	1	1734	neg.	na	–	–	–	5	3
	6	36	7.50	4.90	14.2	neg.	20	0	nd	neg.	na	–	–	–	3	2
4	1	30	8.99	4.32	12.5	1.5	22	5	1014	pos.	na	–	–	++	4	4
	2	nd	nd	nd	nd	nd	nd	nd	2540	neg.	na	–	++	++	nd	nd
	3	40	7.27	4.05	12.1	neg.	32	1	1724	pos.	na	–	++	++	2	2
	4	nd	nd	nd	nd	nd	nd	nd	3420	neg.	na	–	++	++	nd	nd
	5	21	6.45	4..07	12.6	neg.	33	1	1788	neg.	na	–	–	–	1	1
	6	10	6.50	4.35	13.3	neg.	20	0	nd	neg.	na	–	–	+	1	1

The patients were examined before and after the first treatment cycle (day 1, samples 1; day 5, samples 2), before and after the second treatment cycle (day 1, samples 3; day 5, samples 4), and 1 month (samples 5) and 9 months (samples 6) after the end of the second cycle. In addition to laboratory parameters including the amplification of parvoviral DNA derived from serum or synovial fluid, antiphospholipid antibodies (IgG anti-PL: anti-CL, anti-cardiolipin; anti-PS, anti-phosphatidylserine; anti-β_2GPI, anti-β_2-glycoprotein I; –, no reaction; +, positive, ++, strongly positive), doctors' and parents' global assessments of overall disease activity were recorded on a visual analogue scale (VAS) ranging from 0 (healthy) to 10 (severely affected). CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; IVIG, high-dose intravenous immunoglobulin; na, not available; nd, not determined; RBC, red blood cells; SF, synovial fluid; WBC, white blood cells.

were obtained in all samples diluted $1:10^5$ to $1:10^6$. A slight anaemia and an elevated creatine kinase (CK) was observed in patient 2. ANA were not detected in patients 1, 2 and 3. Patient 4 showed a titre of 1:1600 in all samples. ENA were not detectable (Table 2).

Patient 1 responded well to IVIG treatment. At the end of the cycles, viral genomes could not be detected and anti-PL IgG declined. X-ray examinations showed regression of the erosions. Oral steroid and NSAID therapy were gradually decreased to zero. MTX application was continued. During a post-treatment observation period of 15 months, no relapse occurred and the patient was free from disease (visual analogue scale = 1; Table 2). The disability index decreased from 0.13 to 0. The health-related quality of life increased from 75 to 83.3.

Patient 2 did not benefit from IVIG, although the elevated CK (103 U/l) normalized during the first treatment cycle and the number of joints affected with arthritis was reduced from four to two. The elevated ESR and CRP increased slightly. Virus load and the level of anti-PL IgG

declined, but the patient still has recurrent pain in her lower back, wrists, hips and knees. Nine months after treatment the left ankle was swollen, the left wrist was painful and the range of motion was decreased. The disability index increased during the observation period from 0.63 to 1.25 (range: 0, no restrictions; 3, extreme restrictions). The summary score of the KINDL decreased slightly from 62.5 to 59.4.

During the second IVIG treatment cycle and afterwards, patient 3 developed large effusions of the right and left hip followed by recurrent massive effusions of the right knee requiring treatment with TCHA. B19 DNA (10^3 genome equivalents/ml) was amplified from both serum and synovial fluid. One serum sample obtained at the end of the second cycle contained anti-PL IgG (Table 2). ESR (34 mm/h) and CRP (0.9 mg/dl) were moderately increased, but antibody titres against various arthritis-associated infectious agents were unrevealing. Oral prednisolone was increased from 3 mg/day to 25 mg/day (subdivided in two doses of 20 mg in the morning and 5 mg in the evening of each day); treatment with MTX was unchanged. Despite this regimen, two further flares at the right knee occurred and arthroscopic synovectomy was performed. Histology revealed an acute synovitis with massive infiltrations of plasma cells, and B19 DNA was amplifiable from the tissue specimen. After a further massive effusion at the right knee, cyclosporin A was added to the therapeutic regimen (3.5 mg/kg body weight). After two subsequent relapses (left elbow, right hip) the patient reached a disease-free interval lasting 12 months. The disability index before treatment was 0.13; this decreased to 0 after the various therapeutic interventions. The KINDL summary score increased from 62.5 to 75.0.

In patient 4 the effusions of five large joints decreased and painful joint motion disappeared during the first IVIG treatment cycle. No concomitant therapy except continuing naproxen (10 mg/kg body weight) was applied. After the second IVIG cycle only a diminished range of motion of the left calcaneo-cuboid and talo-navicular joints was observed, which further normalized. Virus DNA was not detectable and anti-PL IgG declined, despite a slight increase observed 9 months after IVIG treatment without reappearance of symptoms (Table 2). Fourteen months after the first treatment cycle, naproxen treatment was reduced to 5 mg/kg body weight without disease recurrence. The disability index normalized from 0.25 (minor disabilities) to 0. All activities of daily living were performed without any restrictions. The summary score of the KINDL increased from 78.1 to 86.5. At 15 months after treatment the child was still in full remission.

Discussion

The therapeutic trial with intravenous application of high-dose immunoglobulins resulted in an obvious improvement of symptoms in two of four adolescents with long-lasting, severe polyarticular rheumatic diseases. Previously all patients had failed to respond to intensive immunosuppressive therapy. Despite the development and presence of B19-specific immune reactions, they showed a prolonged state of viraemia or viral persistence in synovial fluid and were incapable of eliminating the virus. This might have been due to an inadequate immune reaction against the viral capsid proteins VP1 and VP2, which have been shown to contain epitopes that induce the production of B19-neutralizing antibodies [9,10]. No defects in the elicitation of either VP1-specific or VP2-specific IgG were observed in any of our patients. However, it is possible that the inability to eliminate B19 virus might be associated with decreased antibody affinities. None of our patients had diseases related to impaired T-cell function. All showed normal immune response to parvovirus B19 proteins as well as to other infectious agents and had normal or elevated immunoglobulin levels, excluding general B-cell dysfunctions. However, the possibility cannot be excluded that the impaired elimination of parvovirus B19 was caused by treatment of the patients with immunosuppressive drugs like MTX or oral steroids over long periods.

In patients 1 and 4 IVIG therapy was capable of eliminating the virus from the peripheral blood. In patient 4 a polyarticular relapse was cured without any concomitant therapy. A similar result had been reported previously for a patient with parvovirus B19-associated anaemia persisting for 10 years [10]. These observations point to subtle defects in specific antibody production and rule out a defect in the T cell immune response. Furthermore, several mechanisms have been proposed to explain the immunomodulatory effects of IVIG. These include modulation of cytokine production and the neutralization of circulating autoantibodies [11]. In addition, we observed a decrease in anti-PL IgG together with a control of B19 viraemia in patients 1 and 4. The benefits of using anti-PL IgG in IVIG therapy in mice have been described previously [12,13]. It might therefore be proposed that in patients 1 and 4 the improvement observed by IVIG was due to the combination of the decrease in both B19 viraemia and anti-PL IgG. It is not clear whether the therapy is capable of inducing a definite cure. Parvovirus B19 DNA has been shown to persist in synovial cells, indicating a state of virus latency [14]. Therefore an occasional reactivation of latent parvovirus B19 resulting in a new production cycle cannot be excluded and might lead to new flares.

In both patients with psoriatic arthritis (patients 2 and 3), IVIG treatment failed. It has to be assumed that the development of psoriatic arthritis is influenced by multiple genetic and environmental factors, including productive viral infections. Recently, parvovirus B19 proteins have

been shown in synovial tissue of patients with psoriatic arthritis [15]. Even though we observed a decrease in virus load, IVIG treatment was not sufficient to improve significantly the clinical course in our two cases of long-lasting rheumatic diseases. This seems not to be a general feature of psoriatic arthritis, because Gurmin and colleagues report three patients with improvement of their arthritis after a single course of IVIG (2 g/kg body weight) [16].

In patient 2 the symptoms of arthritis did improve; however, this patient could not be cured even though parvovirus B19 DNA could not be detected in the serum after the second treatment cycle. This might have been due to a rheumatic disease lasting for more than 8 years, resulting in major joint destructions. The reason for the severe relapse observed in patient 3, with multiple effusions containing free and immunocomplexed B19 particles, remains unclear. IVIG treatment might be associated with an enhanced formation of immunoglobulin complexes, resulting in the induction of complement and cytokines and in the stimulation of inflammatory reactions. In addition, at the end of the second treatment cycle the patient displayed anti-PL IgG in the serum that might have been passively transmitted by the immunoglobulins and might have led to enhanced inflammation [17].

Stahl and colleagues reported successful IVIG treatment of parvovirus B19-triggered oligoarthritis and monoarthritis [8]. We showed the induction of a disease-free interval of 15 months in patients with chronic erosive arthritis. Therefore IVIG treatment might be a therapeutic option for juvenile patients with arthritis and persistent parvovirus B19 production.

Competing interests

None declared.

Acknowledgement

We thank Professor R Lissner (Biotest GmbH, Dreieich, Germany) for the generous donation of Varitect CP immunoglobulin preparations; Mikrogen GmbH (Munich, Germany) for the donation of Recom-Blot and Recom-Well tests; and Karin Beckenlehner and Alexia Herrmann for excellent technical assistance. The work was supported by the European Community (EU contract QLK2-CT-2001-0087).

References

1. Heegaard ED, Brown KE: **Human parvovirus B19.** *Clin Microbiol Rev* 2002, **15:**485-505.
2. Lehmann HW, Kühner L, Beckenlehner K, Müller-Godeffroy E, Heide KG, Küster RM, Modrow S: **Chronic human parvovirus B19 infection in rheumatic disease of childhood and adolescence.** *J Clin Virol* 2002, **25:**135-143.
3. Lehmann HW, Knöll A, Küster R-M, Modrow S: **Frequent infection with a viral pathogen, parvovirus B19, in rheumatic diseases of childhood.** *Arthritis Rheum* 2003, **48:**1631-1638.
4. Nocton JJ, Miller LC, Tucker LB, Schaller JG: **Human parvovirus B19-associated arthritis in children.** *J Pediat* 1993, **122:**186-190.
5. Oguz F, Akdeniz C, Ünüvar E, Kücükbasmaci Ö, Sidal M: **Parvovirus B19 in the acute arthropathies and juvenile rheumatoid arthritis.** *J Paediatr Child Health* 2002, **38:**358-362.
6. von Landenberg P, Lehmann HW, Knöll A, Dorsch S, Modrow S: **Antiphospholipid antibodies in pediatric and adult patients with rheumatic disease are associated with parvovirus B19 infection.** *Arthritis Rheum* 2003, **48:**1939-1947.
7. Tsinalis D, Dickenmann M, Brunner F, Gurke L, Mihatsch M, Nickel V: **Acute renal failure in a renal allograft recipient treated with intravenous immunoglobulin.** *Am J Kidney Dis* 2002, **40:**667-670.
8. Stahl HD, Pfeiffer R, Emmrich F: **Intravenous treatment with immunoglobulins may improve chronic undifferentiated mono- and oligoarthritis.** *Clin Exp Rheumatol* 2000, **8:**515-517.
9. Kurtzman GJ, Cohen B, Hanson G, Field AM, Oseas R, Blase RM, Young NS: **Immune response to parvovirus B19 and an antibody defect in persistent viral infection.** *J Clin Invest* 1989, **84:**1114-1123.
10. Kurtzman GJ, Frickhofen N, Kimball J, Jenkins DW, Nienhuis AW, Young NS: **Pure red cell aplasia of 10 years duration due to persistent parvovirus B19 infection and its cure with immunoglobulin therapy.** *N Engl J Med* 1989, **321:**519-523.
11. Mouthon KS, Spalter SH: **Mechanisms of action of intravenous immunoglobulin in immune mediated disease.** *Clin Exp Immunol* 1996, **104:**3-10.
12. Pierangeli SS, Espinola R, Liu X, Harris EN, Salmon JE: **Identification of an Fcγ receptor independent mechanism by which intravenous immunoglobulin ameliorates antiphospholipid antibody-induced thrombogenic phenotype.** *Arthritis Rheum* 2001, **44:**876-873.
13. Sherer Y, Levi Y, Shoenfeld Y: **Intravenous immunoglobulin therapy of antiphospholipid syndrome.** *Rheumatology* 2000, **39:**421-426.
14. Söderlund M, von Essen R, Haapasaari J, Kiistala U, Kiviluoto O, Hedman K: **Persistence of parvovirus B19 DNA in young patients with and without chronic arthropathy.** *Lancet* 1997, **349:**1063-1065.
15. Mehraein Y, Lennerz C, Ehlhardt S, Venzke T, Ojak A, Remberger K, Zang KD: **Detection of parvovirus B19 capsid proteins in lymphocytic cells in synovial tissue of autoimmune chronic arthritis.** *Mod Pathol* 2003, **16:**811-817.
16. Gurmin V, Rustin MH, Beynon HL: **Psoriasis: response to high-dose intravenous immunoglobulin in three patients.** *Br J Dermatol* 2002, **147:**554-557.
17. Sherer Y, Wu R, Kraus I, Peter JB, Shoenfeld Y: **Antiphospholipid antibody levels in intravenous immunoglobulin (IVIg) preparation.** *Lupus* 2001, **10:**568-570.

Correspondence

Professor Susanne Modrow, Institute for Medical Microbiology, Universität Regensburg, Franz-Josef-Strauss Allee 11, 93053 Regensburg, Germany. Tel: +49 941 944 6454; fax: +49 941 944 6402; e-mail: susanne.modrow@klinik.uni-regensburg.de