long-term safety needs to be established with careful post-marketing data collection from treated patients. This is being conducted in the U.S.A. by the various companies involved in biological immune modulators. Further information will undoubtedly become available over the next several years. The recent warnings from the manufacturers of infliximab (Remicade®) about the threefold increased risk of lymphoma and leukaemia in patients with rheumatoid arthritis and Crohn's disease[2] treated with Remicade® should make those of us treating severe psoriasis cautious about our choices of treatments. A recent report showed that both methotrexate and, to a greater extent, antitumour necrosis factor therapy, increased lymphoma rates in patients with rheumatoid arthritis.[3]

I feel, however, that because of the chronicity and frequently varied therapeutic response of more severe psoriasis, we need as many treatment options as possible. I feel it is also important to explore combinations of many of the existing treatments that we utilize for more severe disease, with the biologicals.[4] It is very important to note Dr Weller's graph comparing ≥75% improvement in the Psoriasis Area and Severity Index with the different treatments. He shows that dithranol plus UVB at 3 weeks gives similar improvement to that obtained at 12 weeks with infliximab—a considerably more expensive and complex treatment given by intravenous infusion, with greater risks of side-effects.

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Parvovirus B19 and systemic sclerosis

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Sir, We read with great interest the recent article by Ohtsuka and Yamazaki reporting a significantly higher prevalence of parvovirus B19 (PV-B19) infection of the skin in patients with systemic sclerosis (SSc) compared with normal subjects and those with other immune-mediated disorders.[1] This report further supports our previous studies suggesting a possible role of PV-B19 in the pathogenesis of SSc.[2–5] We would like to summarize our latest observations on this intriguing subject. Given the possible association of PV-B19 with some rheumatic disorders and its tropism for haematopoietic tissue,[6,7] in 1999 we first demonstrated a significantly higher prevalence of PV-B19 DNA in bone marrow biopsies from unselected patients with SSc compared with controls.[2] Bone marrow may represent a reservoir from which the virus could spread to scleroderma target tissues.[8] Thereafter, we investigated the presence of PV-B19 infection in cutaneous biopsies, as well as in skin fibroblasts and keratinocyte cultures.[3,4] PV-B19 infection was demonstrated in the skin and/or bone marrow biopsies in 76% of patients with SSc.[3] More interestingly, comparable levels of viral DNA were found in all passages of skin fibroblast cultures (from 3/3 to 6/6) using a semiquantitative polymerase chain reaction (PCR).[4] Recently, we investigated the presence of parvoviral infection, tumour necrosis factor (TNF)-α expression and C5b-9 deposition within cutaneous structures in skin biopsies from patients with SSc by means of solution-phase PCR, reverse transcriptase *in situ* PCR, and immunohistochemical and immunofluorescence studies.[5] In particular, the presence of both PV-B19 DNA and TNF-α mRNA was demonstrated in endothelia, fibroblasts, mast cells and perivascular inflammatory cells, along with C5b-9 deposits within the cutaneous vasculature.[5]

Although preliminary, these latest studies gave us new insights into the possible role of PV-B19 in SSc. The disease is characterized by a spectrum of clinical and serological subsets,[9] which could represent the result of a multistep and multifactorial process. Different genetic, environmental and infectious factors may be involved in the pathogenesis of SSc: chiefly, collagen overproduction by altered fibroblasts, and microvascular and immune system alterations.[10,11] Although the actual sequence of events leading to SSc clinical manifestations still remains to be demonstrated, the role of endothelial cell dysfunction in scleroderma microangiopathy, as well as of scleroderma fibroblast alterations in the diffuse fibrotic process, has largely been demonstrated.[10,11] In this scenario, the demonstration of PV-B19 genomic sequences within cutaneous endothelial cells and fibroblasts suggests a possible pathogenetic role of this virus in SSc.[3–5] We can hypothesize that, in genetically predisposed individuals, scleroderma tissue injury may be the consequence of direct PV-B19 cytotoxicity and/or virus-driven autoimmune reactivity, including molecular mimicry mechanisms, as suggested for human cytomegalovirus.[12] In particular, endothelial cell dysfunction and apoptosis could be triggered directly through NS1 parvoviral protein or mediated by TNF-α overexpression. Besides, scleroderma fibroblasts present an abnormally activated phenotype responsible for collagen overproduction, possibly due to deep alterations in

the regulatory pathways controlling connective tissue gene expression. Cultured scleroderma fibroblasts produce increased amounts of type I collagen compared with fibroblasts from healthy subjects; this hyperactivity is maintained for several passages in culture in the absence of potential extracellular activating signals.[10] The ability of PV-B19 persistently to infect scleroderma fibroblasts[4,5] might be responsible for important cell alterations, as suggested by the phenotypic changes observed in normal human synovial fibroblasts infected by PV-B19 *in vitro*.[13]

Finally, the observed high prevalence of PV-B19 in patients with dermatomyositis[1] is also of interest. This finding is not statistically significant probably because of the low number of patients evaluated; however, it confirms previous data suggesting a role for PV-B19 in different autoimmune diseases, including dermatomyositis.[5,7,14] A role for the same virus in both SSc and dermatomyositis is not surprising, considering the clinicopathological similarities and the frequent overlapping between these two disorders.

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Malignant lymphoma presenting as cutaneous granulomatous vasculitis

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Sir, Cutaneous granulomatous vasculitis (CGV) is a rare vasculitis. We report a case of non-Hodgkin lymphoma that presented as CGV. A 55-year old woman was admitted in April 2002 for skin lesions associated with a fever of 38·5 °C, abdominal pain and night sweats. She denied any weight loss or pruritus. She presented with nonpruritic violaceous and erythematous infiltrated papules of 0·5–1 cm diameter in the upper (including palms) and lower limbs. There were no mucosal lesions. Physical examination showed no hepatosplenomegaly or lymphadenopathy. The erythrocyte sedimentation rate was 120 mm in the first hour, C-reactive protein 155 mg L^{-1} and fibrinogen 590 mg dL^{-1}. The white blood cell count was $14{\cdot}3 \times 10^9$ L^{-1} with 85% neutrophils, 0·27% eosinophils and 7·9% lymphocytes. The haemoglobin level was 10·5 g dL^{-1} and platelet count was 391×10^9 L^{-1}. Lactate dehydrogenase was increased at 536 U L^{-1} (normal 240–480) with moderately increased alkaline phosphastase at 348 U L^{-1} (normal 100–280). The level of hepatic enzymes was normal. There was no hypergammaglobulinaemia. An infection screen was negative. Chest X-ray was normal. Serology for *Yersinia*, *Chlamydia pneumoniae*, *C. psittaci*, *C. trachomatis*, *Mycoplasma pneumoniae*, syphilis, *Brucella*, Q fever, hepatitis B and C was negative. Skin biopsy revealed a granulomatous vasculitis. There was poorly organized granuloma constituted by giant cells, and granulomatous angiitis associated with neutrophils, sometimes leucocytoclastic, with discrete epithelioid histiocytes and lymphocytes. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins, antiphospholipids, rheumatoid factor and complement were normal. Antibodies against *Saccharomyces cerevisiae* were positive on one of three occasions. Initially, abdominal ultrasound revealed centimetric coeliac and mesenteric lymph nodes. Empirical treatment with clarithromycin followed by ofloxacin and valaciclovir did not improve the fever. Steroid