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CASE REPORT

Psoriasis: response to high-dose intravenous immunoglobulin in three patients

V.GURMIN, R.MEDIWAKE, M.FERNANDO, S.WHITTAKER,* M.H.A.RUSTIN* AND H.L.C.BEYNON

*Departments of Rheumatology and *Dermatology, Royal Free Hospital, Pond Street, London NW3 2QG, U.K.*

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Summary Treatment of recalcitrant psoriasis and psoriatic arthritis can be challenging, with treatment options limited by drug intolerance or poor efficacy. High-dose intravenous immunoglobulin (hdIVIg) has been used successfully in Kawasaki's disease and idiopathic thrombocytopenic purpura, where it has become the standard treatment. The literature also suggests its positive effect in the treatment of dermatological conditions, such as autoimmune chronic urticaria, atopic dermatitis, scleromyxoedema, dermatomyositis and autoimmune bullous disorders. We report three patients with treatment-resistant psoriasis and psoriatic arthritis who improved with hdIVIg.

Key words: immunoglobulin, psoriasis, psoriatic arthritis

Psoriasis is a chronic, genetically determined and immunologically mediated inflammatory skin disease that affects 1–3% of the world's population.[1] It is a relapsing and remitting condition that may be exacerbated by environmental factors such as trauma, stress and infection.[2] Psoriasis can also affect the nails, scalp and joints. Psoriatic arthritis, a seronegative inflammatory arthritis associated with psoriasis or psoriatic nail disease, affects between 6% and 34% of patients with psoriasis, although it is most prevalent in patients with severe skin disease.[3,4]

There is no cure for psoriasis, but several treatment options exist. These include topical corticosteroids, retinoids, coal tar preparations, dithranol, salicylic acid and vitamin D analogues; phototherapy with ultraviolet (UV) B or UVA plus psoralen; and systemic immunosuppressants such as oral corticosteroids, methotrexate, cyclosporin and acitretin. Hydroxyurea, sulphasalazine, tacrolimus, etanercept and infliximab have also been used in patients who fail to respond to more conventional therapies. However, psoriasis varies greatly in disease extent, severity and response to treatment and can prove difficult to treat.

Correspondence: Dr H.L.C.Beynon.
E-mail: beynon@uk-consultants.co.uk

High-dose intravenous immunoglobulin (hdIVIg) has been used successfully in Kawasaki's disease and idiopathic thrombocytopenic purpura, where it is has become the standard treatment. The literature also suggests its positive effect in the treatment of dermatological conditions such as autoimmune chronic urticaria,[5] atopic dermatitis,[6,7] scleromyxoedema,[8] dermatomyositis[9–12] and autoimmune bullous disorders.[13–16] We report three patients with psoriasis and psoriatic arthritis that was uncontrolled by existing medications who showed an improvement in both joint and skin disease with hdIVIg.

Case reports

Patient 1

A 40-year-old white woman presented with a 10-year history of severe psoriasis and a 5-year history of psoriatic arthritis affecting the hands, feet, elbows, knees, ankles, spine and costochondral joints. Past medical history included Crohn's disease, insulin-dependent diabetes mellitus, hypertension and renal impairment (ethylenediamine tetraacetic acid clearance 76 mL^{-1} min^{-1}) secondary to cyclosporin therapy. Her medications were cyclosporin 175 mg in the morning/150 mg at night, prednisolone 10 mg daily,

tramadol 100 mg four times daily, actrapid 20–26 U three times daily, insulatard 24 U at night, perindopril 4 mg daily, indapamide 1·5 mg daily and cyclical etidronate. Previous psoriasis therapies included methotrexate, intravenous pulsed methylprednisolone, azathioprine, acitretin, mycophenolate mofetil, tacrolimus, hydroxyurea and sulphasalazine, alone and in various combinations. These were discontinued because of poor efficacy or unacceptable adverse effects. Etanercept had been introduced 3 months earlier, after a randomized trial demonstrated its efficacy in psoriasis and psoriatic arthritis.[17] She initially responded extremely well to this treatment, and 6 weeks after commencing etanercept her joint pain had dramatically decreased and she had stopped her regular analgesic medications. The plaques on her arms and legs had also cleared and the skin of her trunk was less inflamed. However, 1 week later, she was admitted to hospital with a life-threatening pneumonitis. The close temporal relationship between the initiation of therapy and the development of sepsis suggested that etanercept may have predisposed to this overwhelming infection, and it was therefore discontinued.

Examination revealed synovitis of the metacarpophalangeal (MCP) joints, wrists, elbows and knees and widespread plaque psoriasis affecting the trunk, scalp and limbs. Ten days earlier, she had been hospitalized and given two pulses of intravenous methylprednisolone 1 g on two consecutive days with little response. She was therefore admitted for hdIVIg 2 g kg^{-1} over 3 days. The infusion was well tolerated and the only complaint was mild headache.

Following the infusion, her joint pain and swelling rapidly reduced and inflammatory markers improved [erythrocyte sedimentation rate (ESR) decreased from 99 to 39 mm in the first hour and C-reactive protein (CRP) from 39 to 9 mg L^{-1}]. She was discharged from hospital on her pre-admission doses of prednisolone and cyclosporin, and improvements in her joint pain and swelling were sustained with monthly hdIVIg. The response of the skin was slower but no less dramatic, and following her third infusion the psoriasis had completely resolved. We intend gradually to increase the interval between hdIVIg doses to reduce the frequency of hospital admissions while maintaining disease control.

Patient 2

A 73-year-old white woman with a 3-year history of psoriasis and psoriatic arthritis affecting the MCP joints, shoulders, hips and knee was referred to the out-patient department. She also had a history of hypothyroidism, depression, mild asthma, hypertension and diverticular disease. Medications included prednisolone 5 mg daily, nifedipine 20 mg daily and salbutamol inhaler as required. Previous psoriasis treatments had been limited to topical and oral corticosteroids as she had refused disease-modifying agents because of their potential side-effects. She was unable to tolerate bisphosphonates or hormone replacement therapy.

On examination, she was cushingoid with a kyphosis secondary to osteoporotic collapse. There was marked synovitis of the MCP joints, left knee and both wrists. Psoriasis was limited to plaques on the extensor surfaces of elbows and knees, and around the umbilicus. Examination was otherwise normal. Laboratory results showed elevated inflammatory markers (ESR 52 mm in the first hour, CRP 61 mg L^{-1}).

She continued to refuse standard therapies for psoriatic arthritis and was admitted to hospital for hdIVIg 2 g kg^{-1} over 3 days. Headache, relieved by simple analgesia, was the only side-effect. A rapid improvement in both her joints and skin and a fall in inflammatory markers (ESR 22 mm in the first hour, CRP 8 mg L^{-1}) was observed. One month later she reported the therapy had been 'life transforming' with resolution of psoriasis and resumption of normal activities.

Patient 3

A 31-year-old white woman presented with a 24-year history of severe psoriasis and psoriatic arthritis affecting the MCP and metatarsophalangeal joints, wrists, knees, ankles, spine and sacroiliac joints. Her medications were sulphasalazine 1 g twice daily, prednisolone 4 mg daily, UVB phototherapy three times weekly and topical clobetasone butyrate 0·05%. Previous erythrodermic and generalized pustular psoriasis had required treatment with hydroxyurea, cyclosporin, mycophenolate mofetil, methotrexate and tacrolimus, with either limited benefit or withdrawal due to drug toxicity.

Examination demonstrated psoriatic nail changes, dactylitis of the toes, MCP synovitis and extensive psoriasis involving 60% of her body surface area. hdIVIg 2 g kg^{-1} was administered over 4 days, as opposed to 3 days, because she experienced low back pain, nausea and headache that responded to a reduced infusion rate and simple analgesia.

Improvement in joint swelling, pain and function was observed. Inflammatory markers also improved, with a fall in ESR from 47 to 5 mm in the first hour, and CRP from 44 to 12 mg L^{-1}. The skin response was less dramatic, with improvement in overall skin appearance but little change in the area affected. We intend to continue monthly hdIVIg, in addition to her pre-admission medications, in an attempt to maintain joint control and improve the psoriasis.

Discussion

We have shown hdIVIg to be effective in the treatment of three patients with psoriasis and psoriatic arthritis. Following the first infusion, a fall in inflammatory markers and an improvement in joint symptoms were observed in all patients, but there was no significant improvement in cutaneous disease involvement in the patients with severe psoriasis (patients 1 and 3). However, in patient 1, remission of psoriasis was achieved after the third infusion, and it is hoped that our other patient will respond similarly to subsequent infusions of hdIVIg.

IVIg has been used for many years to prevent bacterial and viral infections in patients with primary and secondary immunodeficiencies. Higher doses have immunomodulatory effects and have been successfully employed in the treatment of a number of dermatological conditions. In most of these reports, monthly infusions of 2 g kg^{-1} IVIg were administered over 2–5 days. However, a recent review of the dermatological uses of hdIVIg found that the majority of the evidence was limited to anecdotal case reports or uncontrolled trials.[18] Dermatomyositis is the exception, with a single controlled trial demonstrating its positive effect.[9]

In psoriasis, there is keratinocyte hyperproliferation, abnormal differentiation and an inflammatory infiltrate of lymphocytes and neutrophils. Both keratinocytes and T cells produce chemokines and cytokines that are actively involved in the pathogenesis of the disease.[19–22] The importance of these signalling agents in psoriasis is supported by recent studies reporting the efficacy of infliximab and etanercept, inhibitors of tumour necrosis factor (TNF)-α, a cytokine produced in psoriasis.[17,23,24] However, TNF-α also plays a key role in the normal host immune response and these agents may increase the patient's susceptibility to infection. The factors responsible for T-cell activation remain uncertain. Cytokines secreted by keratinocytes following exposure to exogenous stimuli may be responsible for antigen-independent T-cell activation and disease initiation. Alternatively, psoriasis may be an autoimmune disease, with T-cell activation occurring on exposure to self antigens or superantigens.[19,25]

Several mechanisms of action have been proposed to explain the immunomodulatory effects of hdIVIg.[26,27] These include modulation of cytokine and cytokine agonist production, neutralization of circulating autoantibodies and neutralization of pathogens involved in the aetiology of autoimmune disease. It is therefore possible that, given the proposed pathogeneses of psoriasis, hdIVIg exerts its effect on psoriasis through one or more of these processes. Other mechanisms such as inhibition of complement-mediated damage or the blockade of Fc receptors on phagocytes seem less likely.

HdIVIg therapy is a well-tolerated therapy with an excellent safety record. Adverse effects are usually mild and include headache, fever, chills, nausea or vomiting, flushing, changes in blood pressure and low back pain. They are generally self-limiting or can be easily managed by slowing or stopping the infusion, although the administration of hydrocortisone or an antihistamine may occasionally be required. Anaphylaxis is rare. Renal insufficiency, neutropenia and aseptic meningitis are also uncommon.[28] However, hdIVIg is prepared from the pooled plasma of more than 10 000 healthy donors by cold ethanol fractionation[29] and, despite careful selection of donors, viral screening of individual donations and viral inactivation procedures, transmission of blood-borne pathogens remains a possibility.[30,31] Although there is no evidence to suggest that blood products are capable of transmitting new variant Creutzfeldt–Jakob disease, it is an area of potential concern. As a consequence, most hdIVIg is now prepared from non-European blood donations, with the U.S.A. providing most of the serum. However, there has been a subsequent fall in the availability of hdIVIg in Europe and adequate supplies of this product can prove difficult to obtain.

Cost is another important consideration. Drug costs for the treatment of a 70-kg man receiving 2 g kg^{-1} of IVIg (Octagam®, Octapharma, Coventry, U.K.) each month for 1 year are in the region of £45 000 (£30 000 with National Health Service discount). These figures were calculated using information obtained from our hospital pharmacy, but prices are influenced by hospital contracts and vary between individual IVIg products. In-patient costs for a 2–5-day hospital stay each month must also be considered. In comparison, yearly treatment with systemic therapies such as methotrexate 10–15 mg weekly or cyclosporin 2·5–5 mg kg^{-1} daily costs £23–£35[32] and £1668–

£3275,[33] respectively, excluding drug monitoring expenses. The optimum dose and frequency of each hdIVIg infusion remain undetermined and will have an effect on total cost. However, this increased expense must be balanced against improved quality of life, decreased frequency of disease exacerbations and reductions in the dose and associated toxicity of immunosuppressive medications.

As hdIVIg is considerably more expensive than these other therapies, we suggest that it is restricted to an adjunctive therapy for patients with psoriasis and/or psoriatic arthropathy who are resistant to, or intolerant to, existing treatments. We have shown hdIVIg 2 g kg^{-1} over 3 or 4 days to be a well-tolerated and effective adjunctive therapy in the management of three such patients. However, we recognize that prospective randomized clinical trials are necessary to investigate the use of hdIVIg in psoriasis further, particularly in view of the time and high cost involved.

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