Bosentan improves functional class, pulmonary artery systolic pressure, and DLCO in scleroderma patients with pulmonary hypertension: a possible synergy with iloprost.

Lorenzo Beretta, Raffaella Scorza, Nicoletta Del Papa and Antonio Mazzone

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Intraarticular Injection of Infliximab

To the Editor:

Persistent inflammatory knee joint arthritis in patients with rheumatoid arthritis (RA) or spondyloarthropathy (SpA) and good control of disease activity with systemic treatment is a frequent problem for physicians. Usually these patients are treated with intraarticular (IA) injections of corticosteroids, or even with radionuclide or surgical synovec-tomy. We read with great interest the article by Schatteman, et al1, which demonstrated that IA injection of 100 mg infliximab in patients with ankylosing spondylitis (AS) is an effective treatment for knee monoarthritis refractory to IA corticosteroid injections. Their results reinforce published reports of successful treatment of persistent inflammatory monoarthritis in patients with RA or SpA2-5.

We administered a single IA injection of 100 mg infliximab in knee monoarthritis refractory to nonsteroidal antiinflammatory drugs and at least 2 IA corticosteroid injections in 4 patients (mean age 42.1 ± 10.1 yrs) with AS (n = 3) or psoriatic arthritis (PsA) (n = 1). One patient with AS and the patient with PsA followed systemic treatment with combination methotrexate (MTX) and infliximab infusions, and the other 2 patients with AS received monotherapy with MTX 15 mg/week and sulfasalazine (SSZ) 2 g/day, respectively. All patients presented resistant inflammatory arthritis only in one knee joint, while the patients with AS had mild activity of axial disease. Before IA infliximab injection, the patients were examined and the following variables were evaluated: volume of aspirated synovial fluid (ml), pain score (visual analog scale 0 – 100 mm), global assessment of patient and physician (from 0 to 5), degree of swelling and tenderness of knee joint (from 0 to 3), erythrocyte sedimentation rate (ESR, mm/h), and C-reactive protein (CRP, mg/l). There was a significant improvement of all above variables at Week 6 in all patients. Although the knee inflammation had reduced to a great degree, our patients presented relapse of knee monoarthritis some weeks later. There was sustained improvement of knee inflammation by the addition of infliximab infusions to MTX and SSZ in 2 out of 4 patients. In contrast to a recent report2 that demonstrated radiation synovec-tomy with IA yttrium-90 plus glucocorticoids was not more effective than IA treatment only with glucocorticoids, the 2 patients with AS receiving infliximab infusions achieved complete remission of knee monoarthritis with radiation synovec-tomy.

Our results agree with the report by Schatteman, et al. A single IA infliximab injection has a beneficial effect in refractory monoarthritis in patients with AS for a period of some weeks. In the reported 3 cases there were magnetic resonance imaging findings of IA fluid and/or synovial thickening at Week 4, and relapse of knee arthritis after 3 to 4 months from IA infliximab injection. It is interesting to note how the relapse of knee inflammation of the 3 patients was treated.

In contrast to the reported positive experiences with IA infliximab, the results of an uncontrolled study6 did not support the use of IA infliximab for the treatment of persistent knee monoarthritis in patients with RA or SpA and a low general activity of joint disease. Of 6 patients, 5 had a relapse of the knee joint synovitis within 2 weeks and the sixth patient within 6–7 weeks after a single injection of 100 mg infliximab. However, only half of the 6 patients received systemic treatment with disease modifying antirheumatic drugs.

There is also experience in IA administration of etanercept. Bliddal, et al reported efficacy of IA etanercept for active large or small joint synovitis in patients with RA7. Recently, the same authors reported a randomized, controlled, double-blind study of IA injections of 25 mg etanercept vs 40 mg methylprednisolone in RA patients with a flare of arthritis in single joints8. Etanercept was superior to methylprednisolone with regard to reduction of target joint swelling. No differences could be shown between the treatments by patient and physician evaluation.

IA anti-tumor necrosis factor-α inhibitors could be an alternative approach for refractory arthritis in patients with RA or SpA. Large studies are required to determine the selection criteria of patients who are candidates, and the efficacy and safety of this procedure.

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8. Bliddal H, Terslev L, Qvistgaard E, et al. Randomized, controlled,

**Dr. Schatteman replies**

To the Editor:

We thank the authors for their interest in our report and we greatly appreciate their comments. We think their results concur with our findings concerning the more prolonged effect of IA infliximab in refractory monoarthritis in patients with ankylosing spondylitis (AS), compared with IA administration of corticosteroids.

Concerning our 3 patients, the first, a 27-year-old woman, had a relapse of the monosynovitis of the right knee after 4 months taking systemic treatment with SSZ (2500 mg daily). She received a second IA injection with infliximab in this knee and to date there is still a remission of the peripheral arthritis.

The other 2 patients did not have a relapse of their knee arthritis. Due to other complaints (increasing inflammatory low back pain in both patients and plantar fasciitis in the third patient), which did not respond to SSZ or MTX and nonsteroidal antiinflammatory drugs, they received a systemic treatment of anti-tumor necrosis factor α agents (anti-TNF-α), starting about 6 months after the intraarticular injection with infliximab.

At this time they both are in remission, the second patient receiving etanercept and the third patient infliximab.

In reviewing these 3 patients we still think that IA injection with infliximab should be considered only in patients with AS presenting with a monosynovitis of a large joint (and no other symptoms), because it can be a helpful procedure. Patients with refractory monoarthritis and probable AS (in which case intravenous infliximab is not reimbursed in our country) also can be helped by this procedure.

Finally, in our unit we did not obtain good results with radiation synovectomy with IA yttrium-90 in patients with AS, whereas, this procedure proved useful in patients with RA.

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**Seasonal Variation of Primary Neuropsychiatric Systemic Lupus Erythematosus**

To the Editor:

We read with interest the article by Schlesinger, et al, who found a significantly higher prevalence of class V lupus nephritis in winter and spring. Although environmental factors play a role in the multifactorial etiology of systemic lupus erythematosus (SLE), there are conflicting data regarding seasonal variation in SLE activity. In a prospective study, aggravation of systemic disease activity was observed during the sunny season, which was mostly due to nonincidental manifestations (renal disease, impaired values of components of complement or blood counts). Amit, et al, however, found higher scores of photosensitivity during the summer months, but no seasonal pattern in systemic disease activity such as neuropsychiatric (NP) manifestations.

Possible contributing factors to seasonality include changes in activity of the immune system, hormonal effects, and infectious agents. Many infectious diseases show an annual cyclic tendency, with an increase in incidence each winter. Infections may induce apoptosis and subsequently lead to increased levels of autoantibodies. Higher levels of anti-double-stranded (ds) DNA antibodies were found during winter months and showed a correlation with the incidence of parainfluenza virus infections.

A possible role of infections in the pathogenesis of NP symptoms in SLE was suggested by Kowal, et al. In mice, a subset of anti-dsDNA antibodies, identified in 2001 by DeGiorgio, et al, resulted in neuronal damage only when the integrity of the blood-brain barrier was affected by bacterial lipopolysaccharide.

Inspired by this mechanism, we postulated that flares of NP-SLE might also show a seasonal pattern. We propose that most patients with SLE have antineuronal antibodies, but that these antibodies only induce symptoms after infection leads to a breach in the integrity of the blood-brain barrier. An approach to establish a relationship between infectious agents and disease is to demonstrate a seasonal variation in incidence or disease activity. We retrospectively examined if seasonal variation existed in our cohort of SLE patients with primary NP-SLE. Patients were selected from files of our Department of Rheumatology between 1989 and 2003. Diagnosis was based on the American College of Rheumatology (ACR) revised criteria for SLE.

NP manifestations were classified retrospectively according to the 1999 ACR NP-SLE case-definition system. Magnetic resonance imaging (MRI) of the brain was performed in all patients because of active NP symptoms. An experienced rheumatologist assessed disease activity. Flares of NP-SLE were attributed to the month in which the patient underwent the MRI.

Patient characteristics are listed in Table 1. NP syndromes during flares are listed in Table 2: the highest prevalence was observed for cerebrovascular disease, cognitive disorder, headache, and seizures.

Table 1. Characteristics of 48 patients with NP-SLE.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>45 (94)</td>
</tr>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>35.5 (14.5)</td>
</tr>
<tr>
<td>Duration of SLE (years), mean (SD)</td>
<td>5.8 (7.1)</td>
</tr>
<tr>
<td>Prevalence by ACR 1982 criteria (%)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Malar rash</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>34 (71)</td>
</tr>
<tr>
<td>Serositis</td>
<td>24 (50)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>24 (50)</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>48 (100)</td>
</tr>
<tr>
<td>Hematological disorder</td>
<td>36 (75)</td>
</tr>
<tr>
<td>Immunological disorder</td>
<td>35 (73)</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>44 (92)</td>
</tr>
</tbody>
</table>

Table 2. NP syndromes during 61 flares in 48 patients.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barré</td>
<td>1</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>20</td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
</tr>
<tr>
<td>Chorea</td>
<td>2</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>4</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>3</td>
</tr>
<tr>
<td>Plexopathy</td>
<td>2</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Seizures</td>
<td>14</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td>4</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>17</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>3</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
</tr>
</tbody>
</table>
chi-square analysis showed no significant difference from the observed versus the expected number of flares per month (p = 0.160). The higher incidence of NP-SLE flares in January and September may be associated with the habit of postponing hospital visits during Christmas and summer holidays.

It could be argued that not all patients with NP-SLE flares have been included in our cohort, as some patients with mild NP symptoms might not have had an MRI scan. Moreover, patients with varying NP syndromes were analyzed as one group, while in theory, they may represent different disease entities with different pathogenetic factors, thereby creating an artefact. Finally, although our study was one of the largest to date in NP-SLE, it may be underpowered to find a difference (type II error). Nevertheless, we concluded that no seasonal variation in first occurrence or flares of NP-SLE could be established to support the concept that infections are an inducing factor for NP symptoms in patients with SLE.

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Dr. Schlesinger replies

To the Editor:

I thank Dr. Steup-Beekman and colleagues for finding interest in our report1 regarding seasonal variation of lupus nephritis. A significantly higher prevalence in the winter and spring was observed among systemic lupus erythematosus (SLE) patients with class V lupus nephritis (LN), as compared with the summer and fall. A similar trend was seen for seasonal variation of the percentage of patients with class III LN. There is a possibility that the disparity of the monthly and seasonal distribution of various classes of LN may reflect different underlying pathogenic mechanisms that participate in the development of various forms of lupus nephritis. Parallelism between the monthly occurrences of class III and class IV LN may suggest a common trigger.

Seasonal variation has been shown in a number of rheumatic diseases. The incidence of acute gouty attacks is highest in the spring2. The onset or exacerbation of rheumatoid arthritis, the onset of Wegener’s granulomato- sis, antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis, and systemic vasculitis are seen more commonly in the winter3. In determining whether a seasonal variation exists for SLE patients with neuropsychiatric (NP-SLE) manifestations, Steup-Beekman, et al analyzed NP-SLE patients as one group. However, it is known that several of the NP syndromes that were grouped together show seasonality when studied separately. Seasonal variation in stroke incidence and mortality has been extensively evaluated. Seasonal variation (peak stroke incidence in winter) has been found in many countries in the Northern Hemisphere.4-6 Cluster headaches, too, show seasonal variations7. Most attacks occur in January and July, when the days are in turn the shortest and longest. There is also a question of seasonality of seizure activity. Seizure resistance is minimal in autumn and maximum in winter8. Further study is needed to clarify whether a seasonal variation exists for SLE patients with NP-SLE.

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REFERENCES

Bosentan Improves Functional Class, Pulmonary Artery Systolic Pressure, and DLCO in Scleroderma Patients with Pulmonary Hypertension: A Possible Synergy with Iloprost

To the Editor:

We read with interest the article by Joglekar, et al1 in which an improvement in World Health Organization (WHO) functional class2 was observed in patients with systemic sclerosis (SSc) and pulmonary arterial hypertension (PAH) after long-term therapy with bosentan. This improvement was unexpectedly not accompanied by a reduction in pulmonary arterial systolic pressure (PASP), or by an increase in the diffusing capacity for carbon monoxide (DLCO). To broaden the experience in using bosentan in SSc-PAH, we present our observations in a population of Italian patients with SSc treated with bosentan for 12 months, in which the functional improvement was paralleled by an improvement in cardiopulmonary measures.

Twenty patients with SSc3 with a baseline PASP ≥ 45 mm Hg treated with bosentan (62.5 mg bid for 1 month and then 125 bid for 11 months) were considered; all the patients underwent Doppler echocardiogram and complete pulmonary function tests (PFT) at baseline and after 12 months. Fifteen patients (75%) were also receiving concurrent therapy with cyclic intravenous iloprost, as described4. The patients were mostly women (n = 18, 90%) with the limited cutaneous form of the disease (lcSSc = 11, 55%)5 with a mean (± SD) age of 59.3 ± 9.5 years (range 34–74) and a disease duration of 11.4 ± 8.4 (1–30) years. Cardiopulmonary characteristics of the patients at entry into the study and after 1 year are reported in Table 1.

Overall, an improvement in WHO functional class was observed in 12 patients (60%); functional class did not deteriorate in any patient. After 12 months of therapy we observed a significant improvement in the mean WHO functional class, DLCO % of predicted values, and PASP. In patients who improved by at least one WHO functional class, DLCO % of predicted values significantly increased after 1year of treatment (43.4% ± 8.75% vs 51.4% ± 12.6%) compared to patients without functional improvement (36.6% ± 15.4% vs 34.8% ± 14.8%) (p < 0.05, analysis of variance for repeated measures). Subgroup analysis showed that in patients treated with iloprost the variation of DLCO from baseline was significantly higher than in patients receiving only bosentan (22.3% ± 27.7% vs –2.88% ± 13.16%; p < 0.05, Mann-Whitney U-test).

Our data are quite different from those described by Joglekar, et al1, since they did not record any significant change in PASP or DLCO. They speculated that this discrepancy might be due to an increased, but unproven, delivery of oxygen to the exercising muscle. In contrast, our results are more consistent on a pathophysiological basis; previous studies in PAH and other cardiopulmonary diseases have indeed demonstrated that the improvement in oxygen consumption and exercise tolerance is accompanied by a decrease in PASP6,7 and by an increase in DLCO values8. It is noteworthy that in our population only those patients who had a reduction in WHO functional class also had a significant increase in DLCO % of predicted values, indicating that the improvement in the alveolar-capillary membrane diffusing capacity is relevant in PAH-SSc functional responses as well.

Our and Joglekar’s populations of SSc patients were strikingly similar as far as the number of subjects considered, subset, mean age, PFT values, and hemodynamics were concerned. The sole relevant difference was the utilization of intravenous cyclic iloprost4 in the majority of our patients. This would indicate a possible synergy between the 2 drugs, since they differently influence vascular remodelling and the pathways implied in the pathogenesis of PAH9. Moreover, iloprost can reduce the production of endothelin-110, and this property may further contribute to the enhancement of bosentan activity.

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Table 1. Patients’ cardiopulmonary characteristics at entry into the study and after 12 months of therapy. Data expressed as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>12th Month</th>
<th>p1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP, mm Hg (range)</td>
<td>59.5 ± 16.9 (46–120)</td>
<td>47.6 ± 13.93 (30–95)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DLCO, % predicted (range)*</td>
<td>41.55 ± 10.55 (12–55)</td>
<td>47.05 ± 14.81 (13–70)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>FVC, % predicted (range)**</td>
<td>70.4 ± 23.72 (37–111)</td>
<td>73.12 ± 23.03 (37–105)</td>
<td>NS</td>
</tr>
<tr>
<td>WHO functional class, mean</td>
<td>3.2 ± 0.4</td>
<td>2.4 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WHO functional class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>10 (50)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17 (85)</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>

PASP: pulmonary arterial systolic pressure (echocardiogram); DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; WHO: World Health Organization classification; NS: not significant. * Data from 19 patients. ** Data from 17 patients. 1 Paired-samples t-test.

Correspondence

Downloaded from www.jrheum.org on June 24, 2017 - Published by The Journal of Rheumatology


Dr. Riley, et al reply

To the Editor:

The letter by Beretta and colleagues is of great interest. There are 3 principal pathways felt to be of importance in pulmonary arterial hypertension (PAH) including that complicating systemic sclerosis (SSc). These include increased levels of endothelin-1 and diminished production of vasodilatory substances including prostacyclin and nitric oxide, all as a consequence of endothelial injury.

Both short and long term efficacy of monotherapies directed at each of these pathways has been firmly established and there is increasing interest in the potential benefits of combination therapies.

A placebo-controlled trial of inhaled iloprost added onto established background therapy with bosentan has been reported. Inhaled iloprost was associated with a mean additional improvement of 6-minute walk distance of 26 meters along with improvements in New York Heart Association functional class, reduction in mean pulmonary artery pressure, and delay in clinical deterioration. These findings are congruent with prior studies of other prostacyclin-bosentan combinations.

Both Beretta and colleagues’ report describing intermittent intravenous iloprost as well as our own would have been more robust if conducted in a controlled fashion and with more rigorous measures of hemodynamics. Both studies are encouraging, based on their evidence of a durable response in PAH secondary to SSc.

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REFERENCES


Leflunomide for Relapsing Polychondritis: Successful Longterm Treatment

To the Editor:

In March 2002, a 68-year-old woman developed painful tender swelling of the right earlobe. Additively, the left earlobe became inflamed. In August 2002, antibodies to type II collagen were positive. Both earlobes were swollen, erythematous, and tender. Nose was normal. There was no heart murmur. Leflunomide 100 mg was given daily for 3 days, followed by 20 mg daily. Within 2 weeks the earlobes were normal. Leflunomide has been continued more than 3 years at 20 mg qd (or 100 mg every 5 days when only the 100 mg tablets were available) and there has been no recurrence of polychondritis. There were no side effects of leflunomide and complete blood cell count and liver function tests have been monitored regularly. Relapsing polychondritis is a rare disease for which controlled prospective medication trials are lacking. Complications associated with iloprost are insufficient with congestive heart failure and airway collapse with respiratory failure. Standard treatment is prednisolone, with attendant glucocorticoid toxicities. I reasoned that leflunomide, by controlling T lymphocyte mediated autoimmunity, might have efficacy. This has been confirmed. A literature search revealed one report of leflunomide prescription for relapsing polychondritis; that patient was treated only briefly due to an idiosyncratic drug toxicity. Such adverse effects are seen occasionally with leflunomide treatment of other disorders, such as rheumatoid arthritis, and should not be taken to contraindicate use of leflunomide empirically for relapsing polychondritis and other uncommon autoimmune conditions.

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REFERENCE


Dr. Abruzzo replies

To the Editor:

Usually relapsing, the course and severity of relapsing polychondritis is highly variable and its pathogenesis and pathophysiology are unclear. Immune system dysfunction appears to be both T and B cell mediated. Accordingly, many therapies have been utilized with varied effectiveness. In addition to leflunomide, treatments have included glucocorticoids, methotrexate, cyclosporine, cyclophosphamide, azathioprine, and hydroxychloroquine.

The case reported by Handler is of interest for several reasons. First, the subject had a single 5 month course of bilateral earlobe cartilage inflammation that subsided within 2 weeks of treatment with leflunomide as the initial and only therapeutic agent. Disease remission then continued for more than 3 years while leflunomide therapy was maintained.

The probability that disease remission was induced by leflunomide is...
relatively high based on the time course of the events. It is, however, less certain that 3 years of disease remission was dependent upon continued leflunomide treatment. It is inferred that leflunomide was needed to maintain the remission and to prevent relapse of disease. Unfortunately, we are left with uncertainty. Regardless, the report of Handler does address a question presented by the case report of Koenig and Abruzzo. In that report the inflammatory process was chronic and relatively unresponsive to steroids, methotrexate, azathioprine, and hydroxychloroquine. Inflammation of the nasal and auricular cartilages appeared to be responding to leflunomide at 20 and then 30 mg daily when the adverse febrile hematologic reaction developed and treatment was stopped.

It could not be determined whether the adverse reaction was purely idiosyncratic or if the reaction was dependent on some unknown disease factor expressed in relapsing polychondritis, as apparently suggested by Handler. The apparently successful and uneventful course in excess of 3 years of exposure to leflunomide in the Handler case does suggest, as Handler indicates, that the febrile reaction seen in our case was truly idiosyncratic.

It is unfortunate that we are compelled to use case reports to gain insight into relatively rare disease entities that have highly variable courses, and to speculate on therapeutic efficacies. It is probably too much to expect that a multicenter clinical trial would be conducted that would address therapeutic efficacies of potentially effective treatments for relatively rare and chronic or relapsing diseases such as relapsing polychondritis.

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REFERENCES

the use of other TNF-α inhibiting agents. Of note, our patient had been taking adalimumab and etanercept previously without pulmonary symptomatology. Interestingly, TNF-α inhibiting agents have been reported to be beneficial in rheumatoid lung disease. In time, we will likely learn of the range of effects of TNF-α inhibition on RA and lung disease. Until then, clinicians should be aware of the possibility of fatal pneumonitis after infliximab infusion, and should be cautious in its use, especially in patients with preexisting lung disease.

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Thermographic and Symptomatic Effect of a Single Dose of Sildenafil Citrate on Raynaud’s Phenomenon in Patients with Systemic Sclerosis: A Potential Treatment

To the Editor:

Raynaud’s phenomenon (RP) associated with systemic sclerosis (SSc) can be difficult to treat and therefore potential treatments warrant further investigation. We performed a pilot study to see if sildenafil citrate (Viagra™, Pfizer) could provide any benefit in these patients.

We assessed objective skin temperature responses to mild cold challenge post-sildenafil dosing, and subjective symptomatic relief to patients with RP and SSc. RP was defined by characteristic skin color changes, with at least 6 episodes a week. All patients were women, nonsmokers, and postmenopausal or using adequate contraception.

Clinical assessment consisted of items in Table 1. Dynamic thermal imaging of the hands was used to quantify skin temperature changes, and digital temperatures were taken simultaneously. Measurements were performed in a temperature-controlled thermal physiology laboratory (24 ± 1°C). A standardized mild cold challenge test was performed after acclimatizing for 30 minutes. Thermal images of the hands were collected every minute for 15 minutes post-challenge. Individual finger skin temperature responses were processed (FLIR ThermaCAM Researcher) to calculate 2 measures, (1) the area under the curve (AUC) between 1 and 15 minutes post-cold challenge and (2) the percentage recovery to mean baseline temperatures at 15 minutes post-cold challenge. Pre- and post-treatment visual analog scale (VAS) of the hands were also measured. A low VAS indicated a greater feeling of cold discomfort. The patients attended on 2 occasions, being given 50 mg sildenafil on visit 1 and 75 mg sildenafil on visit 2. A baseline cold challenge was performed, the sildenafil was then administered, and after 60 minutes the assessments and cold challenge were repeated. Blood pressure (BP) was measured at 15-minute intervals up to 90 minutes post-dosage.

Five patients fulfilling the American College of Rheumatology criteria for the classification of SScs were recruited. Three patients underwent study at both the 50 mg and 75 mg dosage, 2 declined further participation at the higher dose, one because of a deterioration in SSc, and the other because she had a headache after visit 1. This was the only adverse event reported.

The AUC and percentage recovery to baseline temperatures were calculated for each digit. Of the 5 patients, 3 had clear and significant improvements in digital temperature responses to mild cold challenge (Figure 1). The fourth patient took only 50 mg of sildenafil and showed no significant change in digital temperature responses. Comparisons for Patient 1 could not be made as digital temperatures at 60 minutes were too low for cold challenge testing post-drug. However, this patient did show a finger temperature flush at 30 minutes post-dosing with 75 mg of sildenafil.
VAS improved overall, with median increases in VAS of +10 mm for 50 mg and +15 mm for 75 mg dosages, using post-dose/pre-dose data. Table 1 shows patient details and VAS scores.

There was a small hypotensive effect, following drug administration for both dosages. At 50 mg mean BP dropped from 128/75 mm Hg to 86/67 mm Hg, at 75 mg sildenafil mean BP dropped from 113/73 mm Hg to 100/72 mm Hg. There were no clinical manifestations of hypotension. No patient had digital ischemic lesions at the time of the study.

Our study shows that sildenafil citrate produced quick thermographic and symptomatic improvement in patients with SSc and RP, and was well tolerated. The use of a single dose would suggest that patients with RP could use the drug on an “as required” basis prior to when they knew they would be exposed to cold. This could be useful as RP occurs episodically. It may, however, also be useful to take sildenafil regularly, perhaps starting at a dose of 50 mg bd, especially during periods of cold weather. These results warrant a randomized, controlled study on a larger group of patients with SSc.

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REFERENCES

Table 1. Patient details.

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* Modified Rodnan skin score: uninvolved (0) to maximum involvement (51).

Patients Know It: Hughes Syndrome Is Unique

To the Editor:
A woman named Hughes was referred to St. Thomas’ Lupus Unit for advice regarding the possibility that she had “Hughes syndrome.” The 42-year-old woman appeared very loquacious and meticulous. She arrived with a 3 page, typewritten report describing in detail her symptoms and the numerous encounters she had had with various medical professionals since 2001. Her personal diagnostic hypothesis was that she had Hughes (antiphospholipid) syndrome (APS), but her referring rheumatologist was less than certain about this potential diagnosis. During the consultation, she brilliantly described, with appropriate medical terminology, sudden hearing loss, Meniere’s syndrome, severe headaches, and memory loss, the last 2 symptoms being greatly improved by low-dose aspirin.

When asked their opinion, the students attending our clinics stated that evidence for APS was not convincing: “no history of thromboembolic disease,” “no history of multiple miscarriages,” “cardiolipin antibodies negative.” Clearly, in their view, “Hughes syndrome” sounded more like the patient’s own name rather than the antiphospholipid (Hughes) syndrome. Confusion remained: did she describe “Mrs. Hughes syndrome,” a carefully built pathomimic simulation, or a true Hughes syndrome? Extensive and fixed livedo reticularis of lower limbs (Figure 1) and lupus anticoagulant positive on 2 previous occasions clarified the diagnosis. There was little...
doubt: Mrs. Hughes had nothing else but the antiphospholipid (Hughes) syndrome.

Hughes syndrome is defined by arterial and/or venous thrombosis and pregnancy morbidity in association with antiphospholipid antibodies. However, many other clinical manifestations, such as headache, cognitive impairment, and affective disorders, may be linked to APS. Livedo reticularis, which was included in the original clinical description of the APS, constitutes a major feature of the disease. In the huge experience of St. Thomas’ Lupus Unit, these neurological and dermatological signs are considered as “alternative” criteria for APS. They are even more evocative when they regress taking aspirin and are clearly helpful for the diagnosis on an individual patient basis.

Thus, Mrs. Hughes was right. There are not 2 Hughes syndromes: the only one is the antiphospholipid one. As we reminded our students: always listen to the patient.

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