ARD Online First, published on October 18, 2007 as 10.1136/ard.2007.070227

Autologous Non-myeloablative Hematopoietic Stem Cell Transplantation for Refractory Systemic Vasculitis

HSCT for Systemic Vasculitis

Laisvyde Statkute, MD[1], Yu Oyama, MD[1], Walter G. Barr, MD[2], Robert Sufit, MD[3], Sam Ho, MD[3], Larissa Verda, MD, PhD[1], Yvonne Loh, MD[1], Kimberly Yaung, RN[1], Kathleen Quigley, RN[1], Richard K. Burt, MD[1]

[1] Division of Immunotherapy, [2] Division of Rheumatology, [3] Division of Neurology, Department of Medicine, Northwestern University Medical Center, Chicago, IL,

Abstract word count 249; Text word count 3223

Correspondence:
Richard K. Burt, MD
Division of Immunotherapy
Northwestern University Feinberg School of Medicine
750 N Lake Shore Drive, Suite 649
Chicago, IL 60611
Email: rburt@northwestern.edu

Abstract

Objective

For patients with systemic vasculitis (SV) refractory to conventional therapy, new treatment strategies aimed at aggressive induction of remission and relapse prevention are being sought. We herein report our single center experience in treating 4 patients with refractory SV employing non-myeloablative autologous hematopoietic stem cell transplantation (HSCT).

Methods

Four patients with refractory SV (2 – with neurovascular Behcet's disease, 1 – with neurovascular Sjogren's syndrome, and 1 – with Wegener's granulomatosis) were involved in an IRB and FDA approved phase I clinical trial of high dose chemotherapy and autologous HSCT. Peripheral blood stem cells were mobilized with cyclophosphamide (Cy) and granulocyte-colony stimulating factor. Conditioning regimen consisted of Cy 200 mg/kg and rabbit anti-thymocyte globulin 5.5 mg/kg IV.

Results

All 4 patients tolerated HSCT well without transplant related mortality or any significant toxicity. At median follow up of 28 (range 22-36) months all patients are alive. Three patients (1 each with Behcet's, Sjogren's, and Wegener's) entered a sustained remission at 6, 6 and 24 months, respectively, after the transplant. They had significant decrease in both, disease activity and disease or treatment related damage, measures (Birmingham Vasculitis Activity Score and Vasculitis Damage Index, respectively). All 3 patients who achieved remission discontinued immunosuppressive therapy at the time of transplant and have not required treatment since. One patient with Behcet's disease and positive for HLA-B51 has not improved after HSCT.

Conclusion

We suggest non-myeloablative autologous HSCT is safe and effective treatment for select patients with SV refractory to conventional immunosuppressive therapies.

Introduction

The systemic vasculitides (SV) comprise a broad group of diseases that are characterized by the presence of blood vessel inflammation with intimal proliferation, luminal narrowing and occasional wall necrosis. [1,2] Current SV mortality rates, since introduction of cytotoxic/immunosuppressive therapy, have largely decreased, however, there remains a subset of patients who do not respond, and there is significant disease and/or treatment related morbidity and high relapse rates once treatment is withdrawn.[1-4]

Most validated assessments of prognosis in SV are correlated to disease activity and disease and/or its treatment related damage. [5-7] Additionally, a subset of patients with involvement of major internal organs, especially central nervous system, by the vasculitic process is characterized by severe morbidity and mortality and remains very difficult to treat.[8-10] This supports a need for new treatment strategies for resistant disease in select patients with SV.

Autologous hematopoietic stem cell transplantation (HSCT) has been performed safely and successfully in the last decade to treat multiple severe autoimmune diseases throughout the world.[reviewed in 11] There has been limited case reports of allogeneic and autologous HSCT performed in patients with systemic vasculitis, all from either European registry or Japan.[12-23] We here report results of the first 4 patients involved in a single center phase I clinical trial of high dose non-myeloablative chemotherapy and autologous HSCT for refractory SV.

Patients and Methods

Patients

Four patients with refractory SV were involved in an autologous HSCT trial approved by the Institutional Review Board at Northwestern University, Chicago: 2 patients with neurovascular Behcet's disease (BD), 1 patient – with Wegener's granulomatosis (WG), and 1 patient – with neurovascular Sjogren's syndrome (SS). Inclusion criteria were: 1) a diagnosis of either necrotizing vasculitis, neurovascular Behcet's disease or Sjogren's syndrome with either pulmonary or neurovascular involvement, and 2) disease refractoriness and failure to conventional therapy, defined as Birmingham Vasculitis Activity Score (BVAS) above 20 or recurrent flares with subsequent progressive organ damage while on corticosteroids and at least 6 months of oral or intravenous (IV) cyclophosphamide (Cy) (for necrotizing vasculitis), recurrent oral and/or genital lesions and neurological symptoms while on at least 3 months of oral or IV Cy (for BD), and either recurrent neurologic attacks or progressive pulmonary compromise despite at least 6 months of IV Cy (for SS). All patients signed an informed consent before starting pre-transplant testing. Patient profile including SV manifestations, prior therapies, pre-transplant serology and imaging abnormalities are described in Table 1.

Patient # 1

Twenty five year old white woman developed initial symptoms of crops of lesions on her tongue 7 years earlier. Her symptoms progressed to involuntary facial, neck and arm muscle twitching and intense headaches which would last for hours and were associated with blurry vision and flashing lights. Other symptoms included tinnitus, vertigo, transient left sided deafness, arthritis in her large joints, Raynaud's phenomenon, papular ulcerating lesions on her hands, pustules on her chin, and erythematous rash on chest, buttocks and legs. Due to hematuria she was diagnosed with interstitial cystitis. At the age of 23 she developed left hemiparesis with gradual resolution. Brain magnetic resonance imaging (MRI) performed at that time showed multiple small

subcortical white matter lesions, mostly within frontal lobes. Cerebrospinal fluid analysis was unrevealing with no infection and/or oligoclonal bands detected. Finally, the patient was diagnosed with Behcet's disease and was placed on oral Cy which she took for 3 months, however, her neurological and cognitive decline continued to progress as she developed memory impairment and recurrent disorientation and confusion significantly affecting her daily functioning.

Patient # 2

Forty two year old white woman presented with right optic neuritis (ON), arthralgias, xerostomia, xerophthalmia and fatigue 5 years ago. She was diagnosed with Sjogren's syndrome and treated susscessfuly with steroids and methotrexate until 3 years later, when she developed left ON and transverse myelitis (TM) with lower extremity weakness, paresthesias and neuropathic pain in the upper torso. TM attacks were recurring while on high dose steroids, IV Cy, mycophenolate mofetil, IV immunoglobin and weekly plasmapheresis. Attempts to taper plasmapheresis sessions resulted in TM attacks giving symptoms of lower back pain, urinary frequency, imbalance, lower extremity numbness, and ON flares. Multiple brain and spinal cord MRIs were performed and documented waxing and waning myelitis in the cervical, thoracic and lumbar spine, some with associated enhancement and cord edema.

Patient # 3

Twenty seven year old white woman 3 years earlier developed right ear pain, Bell's palsy and 50 pound weight loss over 2 months. A few months later she manifested a right submandibular mass which was biopsied and revealed granulomatous inflammation. Blood tests revealed positive C-ANCA. The patient was diagnosed with WG. She was started on oral prednisone and oral Cy with improvement of her symptoms. A year later she developed severe headaches, neck pain and blurry vision. She was found to have right orbital and skull base masses. Cy dose was increased and she was treated with pulse steroids. Blurry vision continued; it progressed to diplopia, painful eye movements and significant proptosis. There was no improvement with infliximab infusions. Monthly IV Cy resulted in only a partial response.

Patient # 4

Thirty six year old asian woman 2.5 years ago developed severe pustular folliculitis in her scalp with loss of hair. Her symptoms progressed to pustular and malar rash on her face, and diffuse myalgias and arthralgias, along with painful genital and perianal ulcers, oral ulcerations, conjunctivitis, and keratitis. She also had otitis externa and inflammation of the nasal cartilage. She was treated with oral and IV steroids and azathioprine, levamisole and colchicine without improvement.. A year prior to referral, she developed cognitive dysfunction including memory loss, inability to concentrate, dizziness, severe headaches and myoclonic movements. Brain SPECT (single-photon emission computed tomography) demonstrated decreased blood perfusion in the cortex and thalamus. Brain MRI showed a few focal lesions without enhancement. HLA testing revealed positive HLA-B51. She was diagnosed with neurovascular BD and continued treatment with IV pulse steroids and oral Cy without effect.

Stem cell mobilization

Peripheral blood stem cell (PBSC) mobilization included IV Cy $2g/m^2$ and granulocyte-colony stimulating factor (G-CSF) 10 mcg/kg/day started 72 hours after Cy infusion and continued until completion of apheresis. Apheresis began when white blood cell (WBC) count reached

>1.0x10^9/L and continued until >2.0x10^6/kg of selected CD34+ cells were obtained. Spectra (Cobe, Lakewood, CO) apheresis machine was utilized for all patients.

Stem cell selection

Collected blood products were positively enriched for CD34+ cells using Isolex 300iv2.5 (Baxter, Deerfield, IL) system. Selected products were cryopreserved in liquid nitrogen for approximately 2 weeks until the reinfusion day.

Conditioning regimen

The conditioning regimen consisted of Cy 50 mg/kg/day IV on days -5 through day -1 and rabbit anti-thymocyte globulin (ATG) 0.5 mg/kg IV on day-6 and 1.0 mg/kg/day IV on days -5 through day -1. Hydration and mesna infusion were started before and continued for 24 hours after completion of Cy. G-CSF 5 mcg/kg/day subcutaneously was started on day 0 and continued until WBC engraftment.

Supportive care

Infection prophylaxis consisted of either acyclovir 400 mg or valacyclovir 500 mg three times a day, either ciprofloxacin 750 gm twice a day or levofloxacin 500 mg daily, and either fluconazole 400 mg daily or voriconazole 200 mg twice a day, orally, started the day of admition, and pentamidine nebulizer (300 mg) given once the day of admission for pneumocyctis carinii pneumoniae (PCP) prophylaxis. Upon neutropenia (absolute neutrophil count (ANC) < 0.5 x10^9/L), oral fluoroquinolone was changed to IV cefepime. Antifungal prophylaxis with daily azole and anti-PCP prophylaxis with thrimethoprim / sulfamethoxazole 3 times per week or monthly pentamidine nebulizer were continued for 6 months whereas antiviral prophylaxis was continued for 12 months after the tranpslant.

Red blood cells (RBC) were transfused for Hgb < 8.0 g/L and platelet transfusion was performed for platelet count < 50x10^9/L. All blood products were irradiated, leukoreduced and cytomegalovirus (CMV) safe.

WBC engraftment was defined as the first day of the ANC exceeded 0.5x10^9/L. Platelet engraftment was defined as the first of 3 consecutive days of the platelet count above 20x10^9/L without transfusion support.

Post-transplant follow up

Patients were evaluated at the clinic at 3, 6, and 12 months after HSCT, then yearly thereafter. BVAS and Vasculitis Damage Index (VDI) scoring as well as serological and neuroimaging tests were performed at same intervals.

Outcomes

The primary endpoints of our study were transplant-related toxicity and survival rate; secondary outcomes were change in BVAS and VDI, immunosuppressive medication use, improvement in serologic markers and neuroimaging abnormalities during the post-transplant period. BVAS and VDI are a validated and widely used measure of vasculitis activity.[5-7,24,25] Disease improvement after HSCT was defined as BVAS decline by 25% over baseline. Deterioration was defined as BVAS increase by 50% over baseline. In our study, definition of remission, although arbitrary

but consistent with such in multiple clinical trials,[26-28] included an absence of vasculitis related symptoms and BVAS of 0 with no immunosuppressive therapy.

Results

PBSC mobilization

PBSC mobilization using Cy 2 g/m^2 and G-CSF 10 mcg/kg/day was successful in 3 out of 4 patients; all 3 required only 1 apheresis session each to collect sufficient number (> 2.0x10^6/kg) of CD34+ cells. The patient with neurovascular SS had 3 apheresis sessions performed with suboptimal collection and therefore underwent second mobilization employing G-CSG 10 mcg/kg/day; she required an additional 2 apheresis sessions. Mean number of collected CD34+ cells/kg after selection was 6.86x10^6/kg (range 2.52 – 12.5x10^6/kg). There was no mobilization regimen associated toxicity except 2 events. The patient with neurovascular SS developed right ON flare after the second, G-CSF-only based, mobilization regimen and required pulse IV steroid treatment; symptoms improved to baseline by the time of HSCT. Another event during the peri-mobilization period was the upper extremity phlebitis at the previous peripherally inserted central catheter site in the patient with WG (Table 2).

Early hematopoietic recovery and transfusion of blood products

Median time to WBC and platelet engraftment was 10 (range 10-13) and 10 (range 7-11) days, respectively. Median number of packed red blood cell units transfused were 3 (range 2-4). Median number of required platelet transfusions were 1 single donor (range 0-2) unit and 1 random donor pooled unit (range 0-1) (Table 2).

HSCT toxicities

All toxic events, including neutropenic fever (NF), gastrointestinal adverse effects greater than grade 2 in severity, early and late infections, disease exacerbations, and other unusual events during peri-transplant period, are shown in Table 2.

Survival

At median follow up of 28 (range 22-36) months after the transplant all 4 patients are alive.

Post-transplant disease manifestations and immunosuppressive therapy use (Table 3)

Three patients (1 each with BD, WG and SS) went into remission at 6, 6 and 24 months after HSCT, respectively. One patient with BD is completely asymptomatic without any immunosuppression since HSCT. The patient with neurovascular SS has not had any TM attack which was the primary indication for transplant. Plasmapheresis and mycophenolate mofetil were stopped just before the transplant and she has not required either since. Prednisone was tapered off by 6 months. She continues to have xerostomia and xerophthalmia and residual torso neuropatic pain. The patient with WG gradually became free of headache, right eye pain, blurry vision and proptosis. She was able to discontinue steroids at 14 months and all narcotic medications at 18 months after HSCT. The patient with BD with positive HLA-B51 had clearing of the pustular folliculitis rash on scalp and face initially post-transplant, however, the rash returned within 6 months. She continues to have oral and genital ulcerations and cognitive

dysfunction. After HSCT, the patient has been treated by her local physician with multiple therapies, including IVIG, humira and infliximab, to all of which her symptoms have been resistant.

Disease activity and damage scores

All patients showed marked decrease in BVAS (figure 1). One patient with BD with continuous disease activity has lost follow up. Three patients who entered remission after HSCT had sustained reduction in VDI (Figure 2).

Serologic markers

All rheumatologic blood tests were negative before the transplant in our vasculitis patients except: in the patient with neurovascular SS - positive ANA at titer 1:320, elevated Anti-SSA/Ro at 149 U/ml and Anti-SSB/La at 126 U/ml; in the patient with WG - positive C-ANCA at titer 1:80; and in the patient with neurovascular BD - mildly elevated ANA at titer 1:40. Post-HSCT, the SS patient's ANA persisted but decreased to 1:80 then stabilized at 1:160 at 12 and 24 month follow up, and Anti-SSA/Ro and Anti-SSB/La decreased to 87 U/ml and 24 U/ml, respectively. In the patient with WG, C-ANCA persisted until 12 months but became negative at 24 month evaluation (data not shown). We do not have a repeat ANA result after HSCT for a patient with BD with a positive ANA pre-transplant.

Neuroimaging

In the patient with neurovascular SS, the abnormal signal on the MRI of thoracic spine markedly improved without any evidence of enhancement or edema at 6 and 12 months after HSCT. In the patient with WG, the soft tissue mass in her right orbit remained stable at 6 and 12 months and decreased in size on MRI of the brain done at 24 month follow up. MRI of the brain was unavailable post-HSCT for the patient with BD who was lost to follow up. The other patient with BD in complete remission was unable to undergo serial MRIs post-transplant due to lack of insurance coverage.

Discussion

Up to now, no single center study utilizing a standardized treatment protocol and consistent measures of follow up for patients with SV has been reported in the literature. There have been a few case reports from Europe and Japan on autologous HSCT for patients with refractory SV including BD, WG, Takayasu arteritis, Churg Strauss syndrome, and polyarteritis nodosa, as well as a cord blood transplantation for patients with BD and coexisting myelodysplastic syndrome (MDS), and allogeneic and autologous HSCT for patients with SS and coexisting lymphoma.[12-22] We herein report peri-transplant course and short-term outcomes in 4 patients with refractory SV (BD, WG and neurovascular SS) treated with non-myeloablative autologous HSCT by a standardized protocol. PBSC mobilization utilizing Cy and G-CSF in our patients was safe. Optic neuritis flare in the patient with neurovascular SS which occurred during mobilization using G-CSF without chemotherapy is consistent with disease exacerbations seen in other centers,[29-31] as well as our experience when G-CSF only mobilization was used for the first 4 patients with multiple sclerosis, one of whom developed disease flare.[32] Interestingly, the same patient with neurovascular SS was the only patient who had disease exacerbation corresponding to WBC engraftment after HSCT, a transient TM flare, confirmed by spinal MRI. G-CSF, used

to shorten the neutropenic period, was felt to be the likely culprit. G-CSF may exaggerate cytokine dysregulation which frequently occurs in the rapid recovery phase of hematopoiesis after PBSC transplantation and is clinically recognized as engraftment syndrome. In the literature, G-CSF has been shown to activate preexisting inflammatory eye disease or even induce the disease,[33,34] to cause transient hypoxemia,[35,36] hypercoagulable state,[37] lower threshold of seizure in patients with CNS lupus,[38] and induce flares of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis.[39] For these reasons, patients with autoimmune diseases undergoing non-myeloablative autologous HSCT at our center are mobilized with both, Cy and G-CSF, and being administered G-CSF for faster WBC engraftment starting day +6 of HSCT.

All 4 patients developed neutropenic fever during HSCT, with fever resolution upon WBC engraftment. None of the patients developed culture positive infection or signs of sepsis. Oral thrush in the patient with WG responded well to a change of fluconazole to voriconazole. Moderate-severe gastrointestinal adverse events were rare. Early hematopoietic reconstitution was prompt in all patients.

An interesting immune dysregulation syndrome was observed in our WG patient approximately 2 months after the transplant. The patient presented with multiple evolving vasculitic / thrombotic events: lower extremity (LE) leucocytoclastic vasculitis rash (confirmed on skin biopsy), LE deep venous thrombosis (confirmed by Doppler ultrasound) and complete splenic infarction (found on computer tomography scan). The symptoms corresponded to CMV and EBV reactivation. Interestingly, the ANCA level performed at that time showed very high titers. It is possible that sudden rise in ANCA levels and clinical symptoms were at least partially induced by viral infection. However, reactivation of viruses as a “bystander” cannot be ruled out, and in that case symptoms could be attributed to vasculitis exacerbation related to immune dysregulation after HSCT. A patient described by Daikeler et al[13] had very high ANCA titers following EBV reactivation as well, which declined during treatment with gancyclovir. It has been postulated that a case like this could be supporting evidence for the role of viral infection in the SV etiopathogenesis. Our patient recovered completely (except functional asplenism), following treatment with valgancyclovir, anticoagulation and anti-inflammatory medications.

The effectiveness of autologous HSCT for our first 3 patients has been impressive. The first patient with neurovascular BD had quick disappearance of all vasculitis related symptoms with no immunosuppressive therapy since the transplant. Remission has been sustained for 3 years now and is reflected by BVAS of 0 since 6 months after HSCT.

The patient with neurovascular SS has been a success as no TM flare has developed since HSCT with no need of plasmapheresis and with quick corticosteroid taper. BVAS of 0 has been sustained for 2 years now since 6 months after the transplant. Persistence of sicca symptoms after the transplant in our patient is consistent with reports of autologous HSCT for primary SS that describe malignancy cure but persistence or recurrence of SS. Our patient with a rare manifestation for primary SS - neurological involvement - might be different in that view; pathogenesis of sicca syndrome and vasculitis associated with SS could be distinct so that HSCT could target one but not the other. This supports the concept that the selection of patients for autologous HSCT should be aimed to potentially reversible symptoms, not to specific diagnoses per se.

Improvement and eventual remission in the patient with WG with orbit granulomatous inflammation is consistent with a similar report by Tsukamoto et al.[12] It has taken 1.5 years to taper steroids, and clinical remission in our patient, reflected by symptom-free state and BVAS

of 0, corresponded to ANCA level normalization as well as radiological improvement. It is still controversial whether ANCA are pathogenetic in necrotizing vasculitis. However, serial measurements of ANCA are believed to provide important information about disease activity.[40] A negative ANCA test has been shown to be a useful indicator of remission, although significance of elevated ANCA titers is less certain.[41] A large prospective study of 100 patients with WG showed that rising ANCA levels can signal an impending relapse, but also can occur in patients with no subsequent clinical flare.[42]

Probably the most genetically influenced autoimmune disease is BD. HLA-B51 positivity has been shown to present a much greater risk of developing disease especially in Asian population. Our second patient with neuro-BD did not benefit from autologous HSCT except a mild short-lasting improvement in skin manifestations. Patients like this may be more suitable for allogeneic or cord blood transplantation from a donor devoid of HLA-B51.

In summary, non-myeloablative autologous HSCT for patients with severe refractory SV with neurological involvement has shown to be a safe and effective treatment modality. More patients are needed to confirm this therapy's efficacy and its duration. Patients with refractory BD and positive HLA-B51 marker might be considered for allogeneic HSCT or cord blood transplantation.

References

1) Hoffman GS, Kerr GS, Leavit RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488-498.

2) Gordon M, Luqmani RA, Adu D, Greaves I, Richards N, Michael J, et al. Relapses in patients with a systemic vasculitis. Q J Med 1993;86:779-789.

3) Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticods and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum1999;42:2666-2673.

4) Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.

5) Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, Adu D. Development and initial validation of the vasculitis damage index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997;40:371-380.

6) Exley AR, Carruthers DM, Luqmani RA, Kitas GD, Gordon C, Janssen BA, et al. Damage occurs early in systemic vasculitis and is an index of outcome. Q J Med 1997;90:391-399.

7) Exley AR, Bacon PA, Luqmani RA, Kitas GD, Carruthers DM, Moots R. Examination of disease severity in systemic vasculitis from the novel perspective of damage using the vasculitis damage index (VDI). Br J Rheumatol 1998;37:57-63.

8) Pipitone N, Salvarani C. Systemic vasculitis: state of the art and emerging concepts. Curr Opin Rheumatol 2006;18:1-2.

9) Matteson EL, Gold KN, Block DA, Hunder GG. Long-term survival of patients with Wegener's granulomatosis from the American College of Rheumatology Wegener's Granulomatosis Classification Criteria Cohort. Am J Med 1996;101:129-134.

10) Guillevin L, Le Thi Huong D, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. Br J Rheumatol 1988;27:258-264.

11) Burt RK, Marmont A, Oyama Y, Slavin S, Arnold R, Hiepe F, et al. Randomized controlled trials of autologous hematopoietic stem cell transplantation for autoimmune diseases: The evolution from myeloablative to lymphoablative transplant regimens. Arthritis Rheum 2006;54:3750-3760.

12) Tsukamoto H, Nagafuji K, Horiuchi T, Miyamoto T, Aoki K, Takase K, et al. A phase I-II trial of autologous peripheral blood stem cell transplantation in the treatment of refractory autoimmune disease. Ann Rheum Dis 2006;65:508-514.

13) Daikeler T, Erley C, Mohren M, Amberger C, Einsele H, Kanz L, Kotter I. Fever and increasing cANCA titer after kidney and autologous stem cell transplantation for Wegener's granulomatosis. Ann Rheum Dis 2006;64:646-647.

14) Kotter I, Daikeler T, Amberger C, Tyndall A, Kanz L. Autologous stem cell transplantation of treatment-resistant systemic vasculitis – a single center experience and review of the literature. Clin Nephrol;64:485-489.

15) Hensel M, Breitbart A, Ho AD. Autologous hematopoietic stem-cell transplantation for Behcet's disease with pulmonary involvement. N Engl J Med 2001;344:69.

16) Maurer B, Hensel M, Max R, Fiehn C, Ho AD, Lorenz HM. Autologous haematopoietic stem cell transplantation for Behcet's disease with pulmonary involvement: analysis after 5 years of follow up. Ann Rheum Dis 2006;65:127-129.
17) Rossi G, Moretta A, Locatelli F. Autologous hematopoietic stem cell transplantation for severe/refractory intestinal Behcet's disease. Blood 2004;103:748-750.
18) Yamato K. Successful cord blood stem cell transplantation for myelodysplastic syndrome with Behcet disease. International J Hematol 2003;77:82-85.
19) Tomonari A, Tojo A, Takahashi T, Iseki T, Ooi J, Takahashi S, et al. Resolution of Behcet's disease after HLA-mismatched unrelated cord blood transplantation for myelodysplastic syndrome. Ann Hematol 2004;83:464-466.
20) Rosler W, Manger B, Repp R, Kalden JR, Gramatzki M. Autologous PBPCT in a patient with lymphoma and Sjogren's syndrome: complete remission of lymphoma without control of the autoimmune disease. BMT 1998;22:211-213.
21) Ferraccioli G, Damato R, De Vita S, Fanin R, Damiani D, Baccarani M. Haematopoietic stem cell transplantation (HSCT) in a patient with Sjogren's syndrome and lung malt lymphoma cured lymphoma not the autoimmune disease. Ann Rheum Dis 2001;60:174-176.
22) Minowa R, Miyagawa S, Fukumoto T, Majima T, Shimoyama T, Fujimura Y, Shirai T. Primary Sjogren's syndrome followed by chronic myelogenous leukemia: a case report with a ten year history. J Dermatol 1998:25:460-464.
23) Daikeler T, Kotter I, Tyndall CB, Attarbaschi A, Apperley J, Guardiola P, et al. Haematopoietic stem cell transplantation for vasculitis including Behcet's disease and polychondritis – A retrospective analysis of patients recorded to the European Bone Marrow Transplantation (EBMT) and European League Against Rheumatism (EULAR) databases and a review of the literature. Ann Rheum Dis 2006;Sep 1 (E pub).
24) Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham vasculitis activity score (BVAS) in systemic necrotizing vasculitis. Q J Med 1994;87:671-678.
25) Luqmani RA, Exley AR, Kitas GD, Bacon PA. Disease assessment and management of the vasculitides. Baillieres Clin Rheumatol 1997;11:423-446.
26) Adu D, Pall A, Luqmani RA, Richards NT, Howie AJ, Emery P, et al. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. Q J Med 1997:90:401-409.
27) Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, Le Hello C, Guillevin L. Efficacy of the anti-TNF-alfa antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology 2002;41:1126-1132.
28) De Groot K, Rasmussen N, Bacon PA, Tervaert JWC, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-2469.
29) Snowden JA, Biggs JC, Milliken ST, Fuller A, Staniforth D, Passuello F, et al. A randomized, blinded, placebo-controlled, dose escalation study of the tolerability and efficacy of filgrastim for hematopoietic stem cell mobilization in patients with severe active rheumatoid arthritis. BMT 1998;22:1035-1041.
30) Burt RK, Fassas A, Snowden JA, Van Laar JM, Kozak T, Wulffraat NM, et al. Collection of hematopoietic stem cells from patients with autoimmune diseases. BMT 2001;28:1-12.

31) Openshaw H, Stuve O, Antel JP, Nash R, Lund BT, Weiner LP, et al. Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor. Neurology 2000;54:2147-2150.
32) Statkute L, Verda L, Oyama Y, Traynor A, Villa M, Shook T, et al. Mobilization, harvesting and selection of peripheral blood stem cells in patients with autoimmune diseases undergoing autologous hematopoietic stem cell transplantation. In print for BMT.
33) Vial T, Descotes J. Immune-mediated side effects of cytokines in humans. Toxicology 1995;105:31-57.
34) Parkkali T, Volin L, Siren MK, Ruutu T. Acute iritis induced by granulocyte colony-stimulating factor used for mobilization in a volunteer unrelated peripheral blood progenitor cell donor. BMT 1996;17:433-434.
35) Yokose N, Ogata K, Tamura H, An E, Nakamura K, Kamikubo K, et al. Pulmonary toxicity after granulocyte colony-stimulating factor-combined chemotherapy for non-Hodgkin's lymphoma. Br J Cancer 1998;77:2286.
36) Katoh M, Takada M, Nakayama M, Umeda M. Pulmonary toxicity during granulocyte colony stimulating factor administration and neutrophils. Chest 1996;110:576-577.
37) Canales MA, Arrieta R, Gomez-Rioja R, Diez J, Jimenez-Yuste V, Hernandez-Navarro F. Induction of a hypercoagulability state and endothelial cell activation by granulocyte colony-stimulating factor in peripheral blood stem cell donors. Journal of Hematotherapy & Stem Cell Research 2004;11:675-681.
38) Euler HH, Schwab UM, Schroeder JO. Filgrastim for lupus neutropenia. Lancet 1994;344:1513-1514.
39) Verda L, Luo K, Kim DA, Bronesky D, Kohm AP, Miller SD, Statkute L, Oyama Y, Burt RK. Effect of hematopoietic growth factors on severity of experimental autoimmune encephalomyelitis. Bone Marrow Transplant. 2006 Sep;38(6):453-60.
40) Luqmani RA. Assessing disease activity in the systemic vasculitides. Curr Opin Rheumatol 2002;14:23-28.
41) Gaskin G, Savage COS, Ryan JJ, Jones S, Rees AJ, Lockwood CM, Pusey CD. Anti-neutrophil cytoplasmic antibodies and disease activity during long-term follow-up of 70 patients with systemic vasculitis. Nephrol Dial Transplant 1991;6:689-694.
42) Boomsma MM, Stegeman CA, Van Der Leij MJ, Oost W, Hermans J, Kallenberg CG, et al. Prediction of relapses in Wegener's granulomatosis by measurement of anti-neutrophil cytoplasmic antibody levels: a prospective study. Arthritis Rheum 2000;43:2025-2033.

Figure legends

Figure 1. BVAS before and serially after autologous HSCT in 4 patients with systemic vasculitis. BVAS – Birmingham Vasculitis Activity Score, HSCT – hematopoietic stem cell transplantation.

Figure 2. VDI score before and serially after autologous HSCT in 4 patients with systemic vasculitis. VDI – Vasculitis Damage Index, HSCT – hematopoietic stem cell transplantation.

Table Legends

Table 1. Patient characteristics. HSCT - hematopoietic stem cell transplantation, BVAS - Birmingham Vasculitis Activity Score, VDI - Vasculitis Damage Index, MRI – magnetic resonance imaging, BD – Behcet's disease, SS – Sjogren's syndrome, WG – Wegener's granulomatosis, F – female, IC – interstitial cystitis, CNS – central nervous system, H/A – headache, ON – optic neuritis, B – bilateral, TM – transverse myelitis, R – right, PO – oral, CTX – cyclophosphamide, MTX – methotrexate, IV – intravenous, MMF – mycophenolate mofetil, IVIG – intravenous immunoglobulin, neg – negative, IJV – internal jugular vein, SV – subclavian vein, L - left.

Table 2. Peri-transplant course, including peripheral blood stem cell mobilization, early hematopoietic recovery and HSCT-associated adverse events, in patients with systemic vasculitis. mobilization was by cyclophosphamide at 2 g/m^2 plus G-CSF at 10 mcg/kg/day. HSCT - hematopoietic stem cell transplantation, I-CD34 – infused $CD34^+$ cell dose, WBC – white blood cells, Plt – platelets, RBC – red blood cells, engraft – engraftment, transf – transfusion, U – units, d/c – discharge, BD - Behcet's disease, SS – Sjogren's syndrome, WG – Wegener's granulomatosis, R – right, ON – optic neuritis, L - left, UE – upper extremity, PICC – peripherally inserted central catheter, SD – single donor, RD – random donor, CMV – cytomegalovirus, EBV – Epstein Barr virus, UTI – urinary tract infection, IST – immunosuppressive therapy, TM – transverse myelitis, NF – neutropenic fever, N/V – nausea/vomiting, ATG- anti-thymocyte globulin, LCV – leukocytoclastic vasculitis, LE – lower extremity, L – left, DVT - deep venous thrombosis.

Table 3. Post-transplant clinical course in patients with systemic vasculitis. HSCT - hematopoietic stem cell transplantation, MRI - magnetic resonance imaging, IST - immunosuppressive therapy, d/c – discontinued, BD - Behcet's disease, SS – Sjogren's syndrome, WG – Wegener's granulomatosis, * - patient eventually lost to follow up, TM – transverse myelitis, H/A – headache, L – left, R – right, N/A – not applicable.

Pt #	Diagnosis	Age (years)	Gender	Disease duration (years)	Pre-HSCT manifestations	Pre-HSCT therapy	C-ANCA	P-ANCA	ANA	Anti-dsDNA	BVAS	VDI	MRI findings
1	BD	25	F	7	orogenital aphtous ulcers, arhralgias, skin lesions, IC, CNS involvement (confusion, hemiparesis, myoclonus, H/A)	PO CTX	neg	neg	neg	neg	8	7	multiple subcortical white matter lesions, > frontal lobes
2	SS	42	F	5	recurrent ON B, arthralgias, recurrent TM, torso neuropatic pain, xerostomia, xerophthalmia	MTX, PO/IV steroids, MMF, IV CTX, IVIG, plasmapheresis	neg	neg	1:320	neg	9	2	cervical/thoracolumbar spinal cord lesions with enhancement/cord edema
3	WG	27	F	3	R orbital and skull base mass with eye pain, proptosis, blurry vision, diplopia, painful eye movements, H/A	PO/IV CTX, PO/IV steroids, infliximab	1:80	neg	neg	neg	31	12	low T1 and T2 signal lesion with some enhancement R orbit, enhancing soft tissue along R maxillary sinus and R dorsal clivus region, occlusion of R IJV from jugular bulb to junction of R SV
4	BD	36	F	2.5	HLAB51+, orogenital ulcers, scalp pustular folliculitis, conjunctivitis, keratitis, wt loss, arthralgias, CNS involvement (memoryloss,confusion, myoclonus, H/A)	PO/IV steroids, azathioprine, levamisole, colchicine, PO CTX	neg	neg	1:40	neg	21	4	few foci of increased T2 signal in subcortical white matter, L frontal and parietal lobes

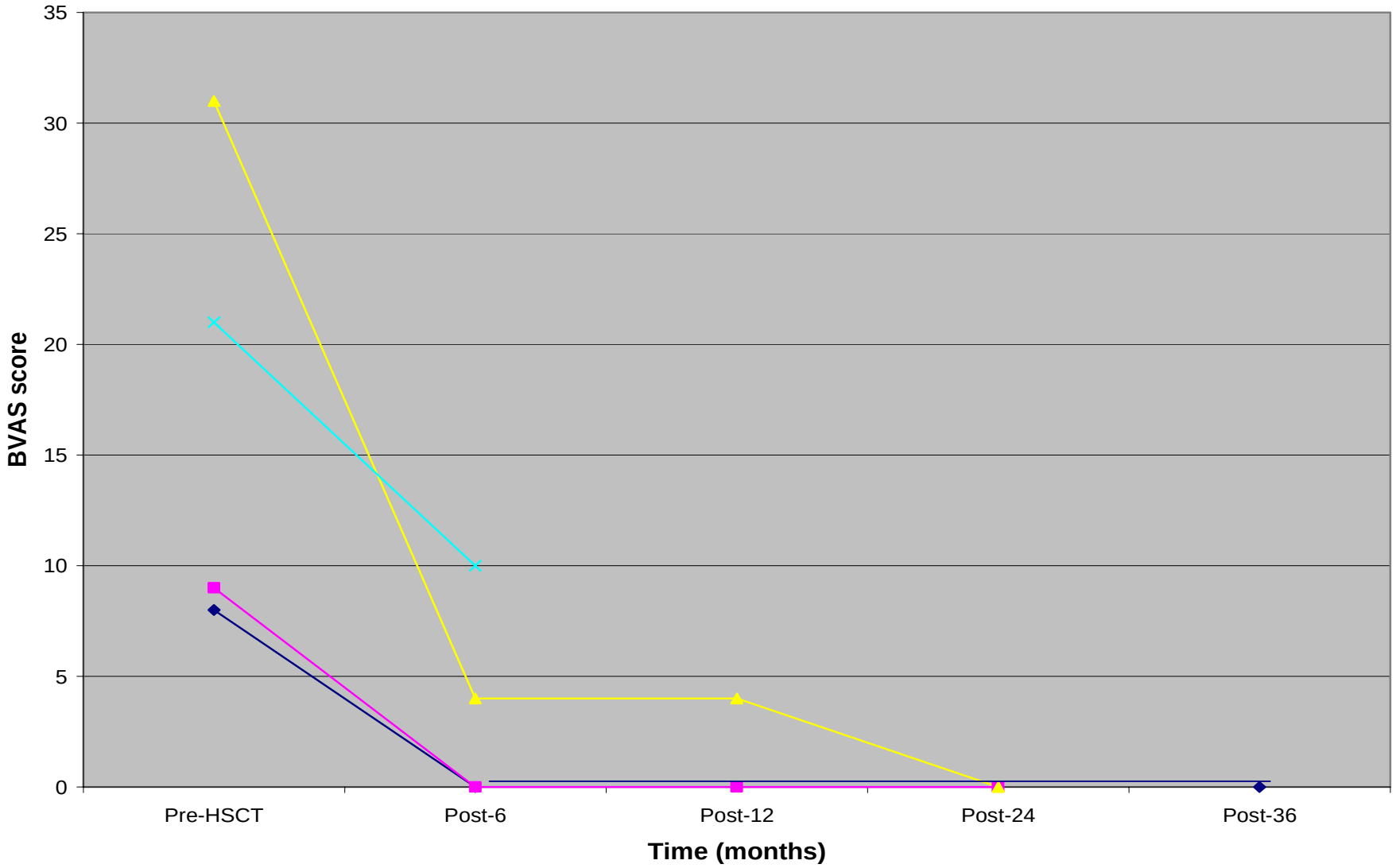
Table 1

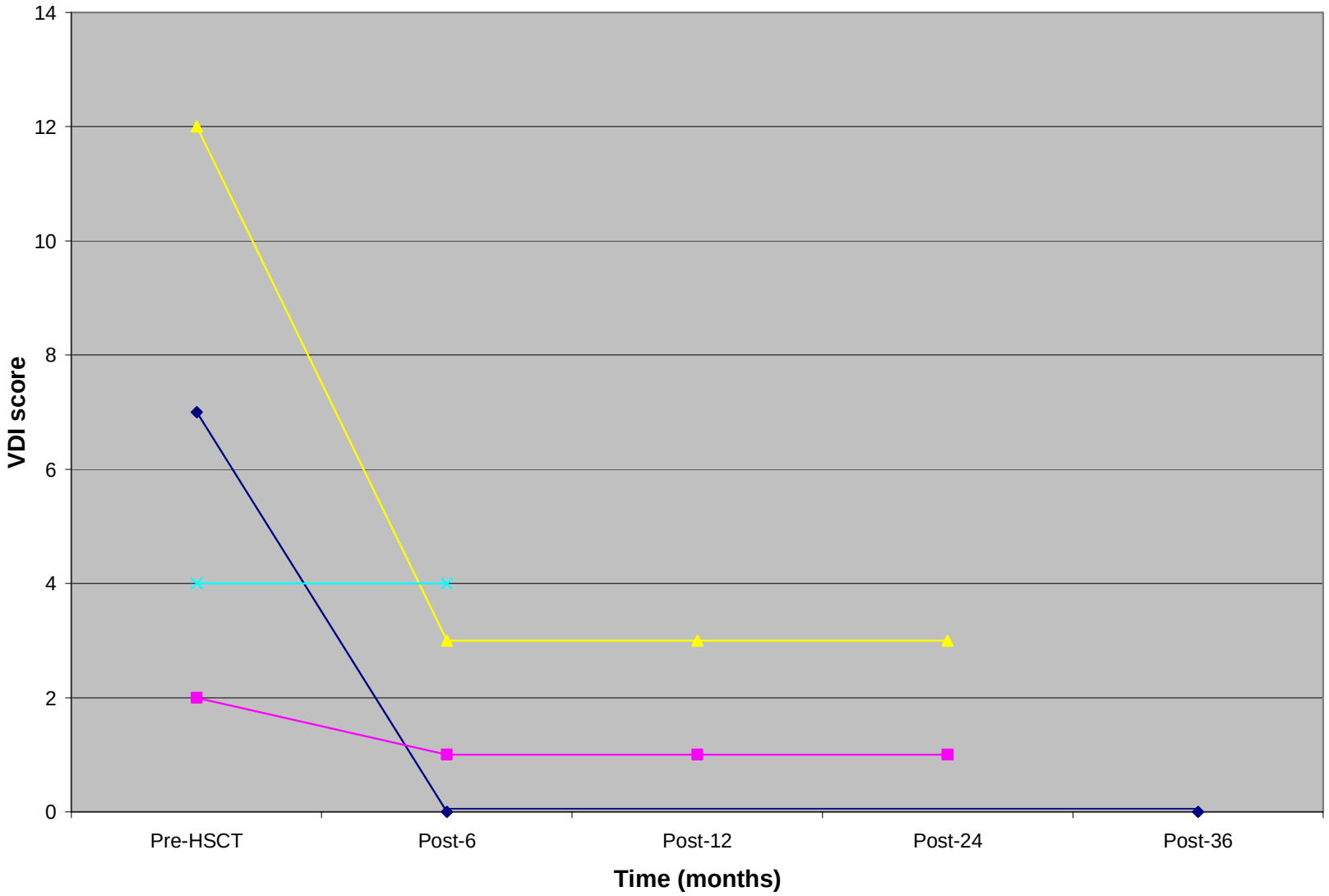
Pt #	Disease	# of apheresis sessions	I-CD34 (x10^6//kg)	Mobilization toxicity	WBC engraft (day)	Plt engraft (day)	RBC transf (U)	Plt transf (U)	Infections		Disease exacerbation	Other toxicities
									Early (before d/c)	Late (after d/c)		
1	BD	1	12.5	none	10	9	4	2 SD / 1 RD	no	no	no	NF N/V grade 3
2	SS	5	2.71	R ON flare after G10 mobilization	10	10	2	1 RD	no	no	TM flare (ataxia, urinary incontinence, torso neuropathic pain) at the end of HSCT	fever with ATG NF
3	WG	1	2.52	L UE phlebitis at previous PICC site	13	11	4	1 SD / 1 RD	oral thrush	CMV and EBV reactivation at 6-8 weeks after HSCT, UTI at 2 months after HSCT	no	NF LCV LE, splenic infarction and L LE DVT at 6-8 weeks after HSCT
4	BD	1	9.74	none	10	7	2	1 SD	no	shingles after further IST	no	NF

Table 2

Pt #	Disease	Follow up (months)	Manifestations (months after HSCT)	MRI findings (months after HSCT)	Remission (months after HSCT achieved)	Relapse	IST use after HSCT	Steroids d/c (months after HSCT)	Narcotics d/c (months after HSCT)
1	BD	36	none	few increased signal foci periventricular white matter, > L frontal lobes (6)	Yes (6)	No	No	N/A	N/A
2	SS	30	no TM recurrence, + xerostomia/ xerophthalmia/torso neuropatic pain	thoracic cord T2 signal markedly improved (6,12)	Yes (6)	No	No	Yes (6)	Yes (12)
3	WG	26	no proptosis/diplopia/ blurry vision/eye pain, + occasional H/A	stable (6,12), decrease in abnormal enhancing soft tissue inferior R obit (24)	Yes (24)	No	No	Yes (14)	Yes (18)
4	BD	22*	pre-HSCT symptom progression	not available	No	N/A	Yes	N/A	N/A

Table 3





Autologous non-myeloablative hematopoietic stem cell transplantation for refractory systemic vasculitis

Laisvyde Statkute, Yu Oyama, Walter G Barr, Robert Sufit, Sam Ho, Larissa Verda, Yvonne Loh, Kimberly Yaung, Kathleen Quigley and Richard K Burt

Ann Rheum Dis published online October 18, 2007