Potential Determinants of Poor Disease Outcome in Socioeconomically Disadvantaged Patients with Rheumatoid Arthritis

To the Editor:

We read with interest the report by Suarez-Almazor and colleagues on the disparities in the time to initiation of disease modifying antirheumatic drugs (DMARD) in patients with rheumatoid arthritis (RA) under public care as compared to those under private care, seen at rheumatology clinics in Texas. The authors reported that the median disease duration at the time of initial DMARD therapy was 1.5 years in the public care setting and 0.5 years in the private care setting (p < 0.0001) and that ethnicity (White vs Non-White) was more important than being under public care (surrogate marker of socioeconomic status) in determining delayed DMARD initiation. The authors conclude that “the potential effects of these disparities on longterm outcomes are unclear, but could be very detrimental in the light of the evidence supporting early onset of DMARD therapy for most patients.” We have recently reported on the timing of DMARD in 359 subjects with RA, 196 public care and 163 private patients, seen in Johannesburg, South Africa. Our results differ from those reported by Suarez-Almazor. Moreover, we recorded not only the timing of DMARD initiation but also the Health Assessment Questionnaire (HAQ-DI), a central outcome variable in RA, as well as lifestyle factors, disease activity and disease severity variables, comorbidities, and treatment characteristics. We therefore believe that our results are of potential interest in the present context. Further, the editorial by Madhok, et al accompanying the article by Suarez-Almazor is informative in the interpretation of our results.

Only 11% of the South African population is Caucasian. Yet, 85% of our private care patients belonged to the latter ethnic group, as compared to only 13% of our public care patients with the majority of them being African (62%) and the remainder Asian (12%) or of mixed ancestry (12%). As applied to the patients of Suarez-Almazor, being under public care reflected socioeconomic disadvantage. Tumor necrosis factor-α blockade therapy and leflunomide were not available in our public care clinic.

In contrast to Suarez-Almazor’s study, the time to DMARD initiation was not significantly different between public care (1.5 yrs) and private care patients (2 yrs) in our study. However, as well documented in previous RA investigations and as further discussed by Madhok and colleagues, we found that socioeconomic disadvantage was associated with more severe RA. Thus, current disease activity and disease severity scores (number of deformed joints) were substantially and significantly higher in public care patients as compared to private care patients. Being under public care was also associated with the comorbidities of obesity and tuberculosis. These differences in current and cumulative disease activity between public and private care patients were present despite overall equally intensive DMARD prescriptions in both settings. Finally, whereas adverse lifestyle factors contribute to socioeconomic health differences as alluded to by Madhok and colleagues, our public care patients smoked and used alcohol less often than did our private care patients.

In contrast to the finding of Suarez-Almazor, et al, that ethnicity rather than socioeconomic disadvantage predicted the delay in DMARD initiation in multivariable analysis, we found that socioeconomic disadvantage rather than ethnicity predicted poor disease outcome (HAQ > 1). As expected, current and cumulative disease activity were further independently associated with poor disease outcome. Suarez-Almazor and colleagues found that the time to glucocorticoid initiation was also more delayed in socioeconomically disadvantaged patients with RA. Although glucocorticoids may retard radiographic progression when used early in the course of RA, the longterm use of these agents in established RA is not supported by currently available evidence. Of interest in this regard, prednisone therapy, which was used 2.6 times more frequently in the public care setting than in the private care setting, was independently associated with a HAQ > 1.

Studies that address differences in characteristics of patients with RA seen in public care versus those seen in private care settings have the potential to contribute to the understanding of poor disease outcome in this disease. Although recently reported evidence indicates the need for early DMARD therapy with its appropriate regular intensification in the case of ongoing disease activity in RA, we found a poorer disease outcome in socioeconomically disadvantaged patients despite a lack of difference in the time to DMARD initiation as well as in the overall prescription patterns of DMARD. Indeed, the potential causes of poor disease outcome in socioeconomically disadvantaged patients with RA are many, often interrelated and complex. As a consequence of our findings and in view of recently reported evidence, in 2005, we established a refractory RA clinic in our public setting in which patients with marked ongoing disease activity are managed separately, seen at more regular intervals, and comprehensively assessed at each visit. Whether tighter disease activity control can be obtained in this manner and in this setting is currently being investigated.

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The patient was a 65-year-old Japanese woman with RA. She was treated in the earliest years with methotrexate (MTX) and prednisolone (PSL). However, disease activity remained high despite those medications. Infliximab (3 mg/kg) was added to PSL and MTX at Weeks 0, 2, and 6, followed by administration every 8 weeks. She initially had a significant decrease in disease activity. Despite its efficacy for symptoms, infliximab was discontinued because interstitial pneumonitis occurred after 6 infusions. After her recovery, she was again treated with MTX, and switched to etanercept. Etanercept proved ineffective, prompting readministration of infliximab after a 14 month interval. The Japanese Ministry of Health, Labor and Welfare had just approved the use of infliximab and etanercept for RA at that time. To prevent infusion reactions, the infusion rate of infliximab was modulated and the patient was premedicated with a combination of H1 and H2 receptor blockers and hydrocortisone. There was no reaction following the first infusion, and swelling and tenderness decreased. However, during the second infusion, she experienced very severe urticaria and pruritus 60 min after the commencement of infusion. Infusion was immediately stopped, and she received 5 mg of diphenhydramine with lactate Ringer’s solution intravenously. The symptoms disappeared completely.

A recent study reported that second infusion 20 weeks or more from the first infusion in CD was a notable risk factor for development of infusion reaction2. Similarly, in Japanese patients with RA, large-scale postmarketing surveillance showed that serious infusion reactions were more commonly observed in participants of the previous clinical trial of infliximab8, and the majority of reactions occurred at the time of the second infliximab infusion after a hiatus of over 2 years (data on file; Mitsubishi Tanabe Pharma, Japan).

The pathophysiology of infusion reactions remains elusive. One possibility is the development of antibodies to infliximab (ATI) — the incidence of ATI has been reported at between 10% and 60%9,10. However, the correlation between ATI and infusion reactions does not appear to be very strong6. Although we were unable to measure its concentration in this case, serum ATI is often not measured because it is undetectable when infliximab is also present in the serum11. Therefore, further investigation is required to establish whether the rate of the infusion reaction is influenced by previous administration of this agent in RA.

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Drs. Baraliakos and Braun reply

To the Editor:

We thank our Japanese colleagues for their comments on our study1. Toki, et al describe an allergic infusion reaction in a patient with rheumatoid arthritis (RA) after discontinuation and retreatment with infliximab, and comment on our published experience in patients with ankylosing spondylitis (AS) who had been treated with infliximab for some years before it was discontinued and later readministered.

The incidence of allergic and other immunologic reactions in response to infliximab therapy has long been studied. This includes antibody formation (antibodies to infliximab, ATI), low infliximab trough levels, infusion reactions, and loss of response. However, the relationship between laboratory measurements and clinical symptoms has not been impressive2. From early data it became clear that the dosage of infliximab has an effect on antibody formation and withdrawal in patients with ankylosing spondylitis. Ann Rheum Dis 2008;67:189-94.

Further, as mentioned by Toki, et al, the role of ATI with respect to development of infusion reactions is not clear. In our study we found ATI in only one patient (without clinical relevance); this may be explained in part by well known technical problems, such as high levels of infliximab in the serum. Correlation of ATI and clinical symptoms such as infusion reactions and loss of response has been reported in patients who were episodically treated with infliximab for active Crohn’s disease3. The patients in our study had not been treated episodically. However, using a different technique for antibody detection, recent data from The Netherlands have suggested a stronger correlation of ATI and clinical symptoms3.

Finally, infliximab in RA is mainly used and approved in combination with methotrexate (MTX) because of superior efficacy4; this is different in AS, where MTX has no proven clinical efficacy on back symptoms5. In the case reported by Toki, et al the first infusions of the patients were performed in combination with MTX, and it is unclear how long this was continued and which dosage was used. Whether the relatively low dosages of MTX used in Japan6 have the same potency to suppress antibody formation is also unclear.

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Abatacept is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte antigen 4 (CTLA4) linked to the modified FC domain of human IgG1. It avidly binds to CD80/CD86 on antigen-presenting cells, blocks the CD28 costimulatory signal, and results in T cell inactivation. It has proven effective in patients with refractory rheumatoid arthritis and efficacious and safe in adults. There are no published reports of its use to treat children for uveitis.

A 16-year-old Hispanic girl with psoriatic arthritis and IgA deficiency was diagnosed with uveitis at 5 years of age. Her right eye had normal visual acuity (VA) of 20/20, while her left eye VA was 20/100 with synchiae, band keratopathy, and cataract. She was initially treated with topical steroids and beta-blocker ophthalmic drops without improvement.

At 6 years of age, she started taking methotrexate (10 mg/m²) and prednisone 10 mg. Cyclosporine was added 1 year later because of persistent uveitis with scarring. She required a penetrating keratoplasty for band keratopathy. She was maintained with cyclosporine, methotrexate, both systemic and topical steroids, and a mydriatic for 2 years. Mycophenolate was then added because of progression of the ocular inflammation. Methotrexate was discontinued.

When she was 8 years old, she was taking cyclosporine 5 mg/kg/day, mycophenolate 500 mg twice daily, prednisone 5 mg, and topical steroids. Infliximab infusions were initiated with stabilization of her eye inflammation. She underwent a trans pars plana vitrectomy for severe vitritis and removal of an inflamed vitreous to reduce inflammation.

Infliximab therapy was discontinued after 1 year because of infusion-related dyspnea and tachycardia. She was maintained with prednisone 15 mg, cyclosporine 5 mg/kg/day, and mycophenolate 500 mg twice daily. Four months later, she developed back and shoulder pain and a scalp and nail rash. Skin biopsy revealed findings were consistent with psoriasis, which improved on topical medication. Magnetic resonance imaging of the spine did not reveal disc protrusion, canal stenosis, or nerve root compression.

Her uveitis remained very active. At 10 years of age, cyclosporine was increased to 7 mg/kg/day, and she was maintained with prednisone 15 mg, mycophenolate 500 mg twice daily, and topical steroid drops. Daclizumab 2 mg/kg intravenously (IV) was given monthly for 6 months without response. She received etanercept (0.4 mg/kg/dose twice/wk) for 3 months when she was 11 years old without improvement in her uveitis. Mycophenolate was discontinued and monthly cyclophosphamide (750 mg/m²) was given for 5 months without effect. She then received 2 infusions of rituximab (600 mg/m²) followed 24 h later by cyclophosphamide (750 mg/m²) over 2 weeks.

Although her uveitis initially improved, she had recurrent inflammation 6 months after her first course of rituximab and cyclophosphamide. At that time, she was taking prednisone 2.5 mg, cyclosporine 4 mg/kg, sulfasalazine 500 mg twice daily, diclofenac 50 mg twice daily, and topical steroids. Two additional infusions of cyclophosphamide and rituximab were given 2 weeks apart without sustained improvement.

Because of her continuing active uveitis and risk of permanent bilateral visual loss, abatacept infusions were started at 10 mg/kg IV (500 mg). Infusions were given at 0, 2, and 4 weeks, and every 4 weeks thereafter. There was a rapid decrease in her ocular inflammation and improvement in her eye disease, resulting in reduction of her medication doses to prednisone 5 mg and cyclosporine 2.5 mg/kg, and discontinuation of sulfasalazine and diclofenac. There have been no increased infections or adverse reactions. After 18 months of therapy her uveitis remains well controlled and she has experienced no complications of the abatacept. There is decreased inflammation of her left eye, and the retina can be visualized through her transplanted cornea. Her visual acuity has been maintained at 20/25 bilaterally.

CTLA4-Ig administration inhibits development of organ-specific autoimmune disease in a variety of model systems (e.g., collagen-induced arthritis, autoimmune oophoritis, and experimental antiglomerular basement membrane autoimmune glomerulonephritis). Experiments have also shown that blockade of the interaction between the B7 family of cell-surface molecules (CD80/86) and CD28 by CTLA4-Fc reduced the incidence and severity of autoimmune anterior uveitis in experimental models. Although the role of peripheral and intraocular T lymphocytes in uveitis is uncertain, this single observation suggests abatacept may represent a useful new alternative and therapeutic approach for treating patients with refractory autoimmune uveitis.

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polychondritis was made. His ear inflammation resolved after prednisone 30 mg daily for 3 weeks. Over the next 5 years he had 2 further episodes of left ear inflammation, pain and swelling of the bridge of his nose (2002), and uveitis (2003). He did not smoke. There was no family history of cardiac disease.

In the summer of 2006, he developed unaccustomed shortness of breath on exertion, fatigue, a recurrence of his left ear inflammation, and diffuse abdominal pain. Pulmonary function tests and a computed tomography (CT) of the chest were normal. He then complained of chest discomfort while walking progressively shorter distances and was referred for urgent cardiac assessment.

Examination was unremarkable with a blood pressure of 120/80. He was in sinus rhythm and breathing comfortably on room air. His body mass index was 21. There were no lymphadenopathy, or joint, eye, or ear abnormalities. Heart sounds were normal with no murmurs or added sounds. Chest examination was normal with no stridor, wheezing, or crackles.

Laboratory investigations revealed normal erythrocyte sedimentation rate, C-reactive protein, troponin, fasting glucose, C3 and C4 levels, and fasting lipid profile. Antinuclear antibodies, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, rheumatoid factor, and antiphospholipid antibodies were negative, and repeated 12 weeks later. An electrocardiogram displayed normal sinus rhythm with Q waves in the inferior leads.

Echocardiogram showed a left ventricular ejection fraction of 53%, mild aortic regurgitation (AR), and normal right ventricular systolic pressure. Cardiac CT showed extensive, asymmetric wall thickening at the aortic root and proximal ascending aorta. There was severe stenosis of the ostium of both right and left main coronary arteries (Figure 1). Cardiac magnetic resonance imaging (MRI) showed subendocardial infarction of the inferior and inferoseptal segments at the base and mid-cavity (Figure 2). Abdominal CT revealed 50% narrowing of the proximal right external iliac artery.

He was initially treated with prednisone (1 mg/kg/day), oral methotrexate (titrated up to 25 mg weekly), and a beta blocker. His angina improved over the next several days. He received 3 intravenous infusions of infliximab (5 mg/kg/dose) over the next 2 months. Although he was asymptomatic at 12 weeks into therapy, an exercise stress test (Naughton protocol) was positive. The patient refused early catheterization and surgery in favor of further immunosuppressive therapy. Infliximab and methotrexate were discontinued, and he began taking oral cyclophosphamide 100 mg daily.

Cardiac catheterization and aortography in February 2007 showed critical left main stem ostial disease, modest disease in the mid left arterial descending, and moderate aortic regurgitation. The right coronary artery was too tight to be cannulated. Elective surgery was carried out in April 2007 with triple coronary artery bypass and composite replacement of the aortic valve and ascending aorta. Pathological examination showed the presence of a pan-aortitis with a perivascular infiltrate, predominantly of lymphocytes, macrophages, and few plasma cells (Figure 3).

The patient recovered uneventfully from surgery, remains asymptomatic, and has returned to work. He is being maintained with a tapering dose of prednisone, methotrexate 20 mg weekly, atorvastatin, acetylsalicylic acid (ASA), metoprolol, and coumadin. Echocardiogram 6 months post surgery showed mild improvement in left ventricular function.

Vasculitis is estimated to occur in 11-56% of patients with RP and has a 5 and 10 year survival probability of 74% and 55%, respectively. A literature review indicates that aortic valve (AV) involvement occurs in 4-6% of patients with RP, and severe regurgitation is a frequent indication for surgical intervention. Mortality secondary to cardiovascular manifestations is estimated at 18%, second only to laryngotracheal involvement. Coronary ostial lesions are uncommon and presumed related to involvement of the adjacent aorta. The main histological findings are a lymphocytic infiltration around the vasa vasorum of the outer media with loss of elastic tissues. To our knowledge there are only 4 other cases reported in the literature.

Reported medical management of RP with coronary vasculitis has included high doses of corticosteroids, methotrexate, and/or cyclophosphamide. We chose infliximab prior to cyclophosphamide because of anecdotal reports and personal success in the treatment of severe RP. Despite aggressive medical management, most patients with cardiovascular involvement require surgical intervention because of severe, irreversible structural damage.

Reported surgical outcomes for cardiac manifestations of RP are limited. Postoperative complications, including prosthetic dehiscence and perivalvular leakage, are in part due to corticosteroid therapy causing aortic tissue fragilization. It is recommended that all patients...
requiring surgery for disease involving the ascending aorta or sinuses of
Valsalva have a prophylactic Bentall-type operation with composite aortic
graft, along with coronary button re-implantation technique. All patients
need close followup because of the relapsing nature of the disease.

The fact that the clinical presentation of cardiovascular manifestations
usually occurs late, and there is often no elevation in inflammatory mark-
ers, makes it extremely difficult to detect such lesions and to monitor dis-
ease activity. A favorable outcome is dependent on awareness, early diag-
nosis, aggressive medical treatment, and surgical correction when stable.

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Figure 2. Cardiac MRI, short axis oblique projection of the basal left ventricle (LV), post
gadolinium using a prepared inversion recovery gradient echo pulse sequence. There is a well
defined area of subendocardial enhancement (arrow) in the territory of the right coronary
artery, involving 60-75% of the thickness of the infero-septal wall of the LV consistent with
subendocardial infarction. RV: right ventricle.

Figure 3.A. Surgically excised segment of aorta showing an area of ulceration with a thrombus seen in
the base of the ulcerated region. The surrounding aortic intima appears grossly unremarkable.
B. Section of aorta from the grossly ulcerated area seen in A. There is a break in continuity of the aorta, with the
gap bridged by new fibrovascular tissue (arrow). This area shows thick walled arteries and an infiltrate
of mononuclear cells. The adjacent area shows features of panaortitis. I: intima; M: media; Stain: Movat
pentachrome, original magnification ×2.5.
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Is Carotidynia Syndrome a Subset of Vasculitis?

To the Editor:

Carotidynia is the syndrome characterized by unilateral neck pain initially described by Fay1 in 1927. The clinical finding is tenderness over the carotid bifurcation and pain aggravated by movement of the neck without structural abnormality. The symptom has a short duration of about 2 to 4 weeks, suggesting self-limited disease. The occurrence and cause of carotidynia are unknown.

We describe the case of a 74-year-old woman with diabetes mellitus, hyperlipidemia, and hypothyroidism who developed carotidynia. She consulted us complaining of acute pain and swelling at the left side of her neck and stiffness from the left side of her neck to shoulder in October 2007. She had appeared a few days earlier without any previous infectious symptoms or trauma. The physical findings showed tenderness on palpation from her left carotid bifurcation to internal carotid artery, which was swollen about 2 cm. Her body temperature was 36.3°C. The presence of a carotid bruit was unclear. Laboratory findings showed normal peripheral blood cell counts. High-sensitivity C-reactive protein (hs-CRP) was slightly elevated at 0.367 mg/dl (0.046 mg/dl at 6 mos previously) and serum amyloid A protein (SAA) was slightly elevated at 10.5 µg/ml (normal range is less than 8.0 µg/ml). Hepatitis B surface-antigen and hepatitis C virus-antibody tests were negative. ELISA for myeloperoxidase-antineutrophil cytoplasmic antibodies (ANCA) and PR3-ANCA were negative. Ultrasonography (US) of the carotid artery showed a hypoechoic wall thickening of the proximal left internal carotid artery (Figure 1A). Wall thickening was found in 2 different layers of the vessel wall with slight narrowing of the affected vessel. Magnetic resonance imaging (MRI) of the carotid artery showed the following findings: (1) mildly increased intensity in internal carotid sheath was seen on T2-weighted images, (2) fat-suppressed T2-weighted MRI and gadolinium-enhanced T1-weighted MRI showed homogeneous enhancement of the left internal carotid wall including soft tissue around arterial wall (Figures 2A, B), and (3) MR angiogram showed no significant carotid lumen stenosis (image not shown). According to the criteria for carotidynia as defined by the International Headache Society (IHS) classification of 1988, we diagnosed her condition as carotidynia. She was treated with a nonsteroidal antiinflammatory agent for 2 weeks. Her neck pain gradually diminished and was resolved 2 weeks after the onset. Four weeks later, her ultrasonography test showed significantly fewer abnormal findings (Figure 1B). Further, the levels of hs-CRP and SAA were also reduced to 0.020 mg/dl and 2.5 µg/ml, respectively.

Carotidynia indicates not only unilateral neck pain but also various symptoms including headache, sore throat, jaw claudication, dysphagia, malaise, nasal congestion, and lacrimation. We should consider the following diseases and syndromes as differential diagnoses: arterial dissection, cervical disk disease, cluster headaches, myofascial pain syndrome, giant aortic aneurysm, and relapsing polychondritis. For the latter, we examined the Mayo Clinic records and the literature review and found 33 patients identified through these sources. Among them, 2 patients were treated with infliximab for refractory carotidynia. In 1 patient, the symptoms diminished and in the other they disappeared. The symptoms in the latter patient resolved in 2 weeks. We report here a 74-year-old woman who was treated with a nonsteroidal antiinflammatory agent for 2 weeks. The symptoms diminished in 2 weeks. A sustained response to infliximab in 2 patients with refractory relapsing polychondritis. J Rheumatol 2003;30:1394-5.

Figure 1. Ultrasonography of a longitudinal section of the proximal left internal carotid artery. A. Before treatment. Hypoechoic wall thickening of the proximal left internal carotid artery. B. Followup 4 wks later, showing fewer pathological findings.

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cell arteritis, acute pharyngitis, peritonsillar abscess, acute sinusitis, thyroïditis, sialolithiasis, mononucleosis, and cervical adenitis. In our case, these diseases were ruled out.

On the other hand, the second International Headache Society classification in 2004 no longer refers to carotidynia as an independent pathological entity. That is, they concluded that carotidynia was a not validated entity, but a syndrome of a unilateral neck pain.

Currently, the view prevails that the conventional concept of carotidynia as having no structural abnormality should be removed from the previous classification system. These findings of carotidynia on US, computerized tomography (CT), and MRI examinations have recently been reported. In our case, the findings on US and MRI were compatible with the findings of previous reports.

The positive inflammatory findings have not been previously described in carotidynia. However, nonspecific vascular inflammation has been demonstrated histologically in carotidynia and both hs-CRP and SAA levels were slightly elevated in the far-advanced stage of carotidynia in our case, indicating the existence of acute inflammation. Indeed, the measurement of hs-CRP is beginning to be considered as a trivial inflammatory marker of arteriosclerosis, and relative risk of cardiovascular event is associated with increase of hs-CRP. That is, hs-CRP > 0.2 mg/dl is a high risk factor of cardiovascular event. Our most important finding was that the changes of symptoms and images and those of inflammatory findings of hs-CRP and SAA were parallel. Recently, a new disorder concept of “idiopathic carotiditis” was reported. These authors proposed new criteria and our case fulfilled their criteria.

Considering the above, our findings support the hypothesis that carotidynia could be a distinct disease entity, caused by inflammation. In other words, this means that carotidynia may be a subset of vasculitis. We emphasize the importance of measuring hs-CRP and SAA as characteristics of disease activity in patients with carotidynia.

Carotidynia is an age-old disease entity and may be more prevalent than previously thought. We must investigate further cases of carotidynia in order to elucidate its pathophysiology and mechanisms of development, and the association between carotidynia and vasculitis.

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