

Correspondence

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact: The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M4W 3C7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.

Sex Differences in Giant Cell Arteritis

To the Editor:

We read with interest the observations of Dr. Nir-Paz and colleagues regarding sex differences in clinical features of giant cell arteritis (GCA)¹. In this hospital based study of 88 patients (59 women, 29 men) diagnosed with GCA during hospitalization (excluding information about a further 55 patients who apparently were diagnosed with GCA prior to the hospitalization), one principal conclusion of the authors is that ophthalmic involvement, specifically blindness, is more common in men (11/29 men had some form of blindness in contrast to 8/59 women). The authors acknowledge that they examined a referral population, with sicker, multi-morbid patients more likely to be referred to hospital. As GCA is currently typically diagnosed in the outpatient setting, likely more patients with atypical presentation will not be diagnosed with GCA until they are hospitalized. Their findings appear, therefore, likely to apply mainly to a subset of patients with GCA, namely, those diagnosed in hospital. Admission rate (Berkson) bias will further limit the validity of this study when making any assumptions about sex dependent disease characteristics of GCA. Hospitalization rates differ for different diseases (e.g., higher for cerebrovascular accident (CVA), diabetes mellitus, and renal failure), rendering possible associations of respective diseases with GCA spurious if the prevalence of these diseases already shows a sex difference in the general population. Nir-Paz, et al found an increased prevalence of CVA, non-insulin dependent diabetes mellitus, and chronic renal failure in the male hospitalized patients with GCA compared to female patients, which may be just a reflection of the Berkson bias. We are further not given any details about when blindness occurred, and whether this was necessarily related to GCA. As blindness is associated with CVA even independently from GCA, but also with diabetes mellitus and arterio/atherosclerosis, it is important to know whether and how eye involvement with GCA was ascertained.

Population based cohort studies remain the gold standard in establishing disease characteristics in epidemiologic research. The authors are wrong when they state that "differences in the clinical presentation between men and women have not been reported". Machado, et al reported² an increased frequency of headache in women compared to men (81% vs

56%) as the only statistically significant difference by sex in the clinical manifestations of GCA in a 35-year population based study of 94 patients with GCA in Olmsted County, Minnesota, USA. There was a tendency for an increased frequency of blindness (partial and complete) in males (19% vs 12%), which was not statistically significant. The authors noted increased rates of diabetes mellitus, CVA, and chronic renal failure in patients with GCA compared to rates in the community. We are not told if the comparisons were made with hospitalized community patients, as would be most appropriate, or the overall community prevalence, which would likely be lower.

To corroborate their assumptions about sex related differences of GCA, the authors refer to Brack's study³ of a referral population with large-artery GCA, which had a lower percentage of females in the control group of patients with cranial GCA compared to the cases with large-vessel GCA. They are unaware of or ignored the study of Klein, et al⁴ regarding large-artery involvement in GCA, another referral population study that did not find a difference in the incidence of large-artery involvement by sex. We were unable to find a difference of large-artery involvement by sex in a population based study of 168 patients with GCA (unpublished data).

The study by Nir-Paz, et al has only limited value for making assumptions about sex dependent disease characteristics of GCA due to methodological limitations. Without clear acknowledgment of these limitations, their findings may be misleading. We suggest that an explanation for their findings may be related more to study methodology rather than true sex differences in the manifestation of GCA, and certainly will require further confirmation. Should their observations hold true in population based studies, or at least referral population studies that are not confounded by Berkson bias, this would be a valuable contribution to our understanding of GCA. Differences from our observations in population based studies of predominantly Caucasians of Northern European ancestry could be explained by ethnic differences compared to the population studied in Israel. But any such conclusions are premature in view of the limitations of the study of Nir-Paz, et al.

Finally, we point out that the first description of GCA by Horton, et al was not in 1934 as cited by the authors, but in 1932⁵.

DIRK M. NUENNINGHOFF, MD; GENE G. HUNDER, MD; ERIC L. MATTESON, MD, MPH, Division of Rheumatology, Mayo Clinic and Mayo Graduate School of Medicine, 200 1st Street SW, Rochester, Minnesota 55905, USA.

REFERENCES

1. Nir-Paz R, Gross A, Chajek-Shaul T. Sex differences in giant cell arteritis. *J Rheumatol* 2002;29:1219-23.
2. Machado EB, Michet CJ, Ballard DJ, et al. Trends in incidence and clinical presentation of temporal arteritis in Olmsted County, Minnesota, 1950-1985. *Arthritis Rheum* 1988;31:745-9.
3. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum* 1999;42:311-7.
4. Klein RG, Hunder GG, Stanson AW, Sheps SG. Large artery involvement in giant cell (temporal) arteritis. *Ann Intern Med* 1975;83:806-12.
5. Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of temporal vessels. *Mayo Clin Proc* 1932;7:700-1.

Dr. Nir-Paz and Dr. Chajek-Shaul reply

To the Editor:

We thank Dr. Nuenninghoff, et al for their interest in our article¹. As they assert and as we stressed in our article, our cohort was hospital based, and as such is biased. Nevertheless, this bias allows us to concentrate on the sicker patients with more complicated GCA. As we stated, while this may influence the validity of the results ("Berkson bias"), factors promoting

admission may also serve as important risk factors for disease severity and progression. In order to eliminate this confounder we compared background disease prevalence (non-insulin dependent diabetes mellitus, cerebrovascular accident, and renal failure) between our population of patients with GCA to a population of the same age selected randomly from the electoral register in Jerusalem². Nuenninghoff, *et al* have suggested that hospital controls should be used, but that might have falsely lowered the differences between the cases and controls³. A random community sample such as we selected is an accepted way of handling such bias, especially in the elderly⁴.

As we state in the introduction to our article (references 6–9), when looking carefully at the details of several articles dealing with GCA, one can find hints of sex differences. An additional article addressing this issue was recently published⁵. The article by Machado, *et al*⁶ supports our observation of an increased tendency to blindness in male patients. They also found that females had significantly more headaches than males.

We did not quote the article by Klein, *et al* from 1975⁷ concerning large-artery involvement since diagnostic modalities at that time were less advanced than at present, possibly engendering underdiagnosis of large-artery involvement. It should be noted that sex related difference of arterial involvement is presently only an assumption, and not proven.

In all cases when blindness was noted, it was ascribed only to GCA and not to other factors.

Indeed the first report of Horton, *et al*⁸ was in December 1932, but we preferred to quote the article published a little more than one year later⁹ (March 1934), in which the authors present a more detailed report of 2 patients with GCA, instead of the early short report of 1932.

We agree that prospective population based controlled cohort studies are the best method for evaluating clinical presentation and progression of diseases. More important, it seems that for clarifying clinical factors such as sex differences, larger studies are needed in addition to permitting meaningful analysis of the influence of other diseases. Probably multinational studies will be needed too.

We feel that although our study has limitations (as stated in our discussion), it still points to true sex differences among the population with GCA.

RAN NIR-PAZ, MD; TOVA CHAJEK–SHAUL, MD, Department of Medicine, Hadassah University Hospital, Jerusalem, Israel.

REFERENCES

1. Nir-Paz R, Gross A, Chajek-Shaul T. Sex differences in giant cell arteritis. *J Rheumatol* 2002;29:1219-23.
2. Stessman J, Cohen A, Ginsberg GM, et al. The Jerusalem seventy-year-old longitudinal study. I: Description of the initial cross-sectional survey. *Eur J Epidemiol* 1995;11:675-84.
3. Feinstein AR, Walter SD, Horwitz RI. An analysis of Berkson's bias in case-control studies. *J Chron Dis* 1986;39:495-504.
4. Robertson SJ, Grufferman S, Cohen HJ. Hospital versus random digit dialing controls in the elderly. Observations from two case-control studies. *J Am Geriatr Soc* 1988;36:119-23.
5. Narvaez J, Nolla-Sole JM, Valverde-Garcia J, Roig-Escofet D. Sex differences in temporal arteritis and polymyalgia rheumatica. *J Rheumatol* 2002;29:321-5.
6. Machado EB, Michet CJ, Ballard DJ, et al. Trends in incidence and clinical presentation of temporal arteritis in Olmsted County, Minnesota, 1950-1985. *Arthritis Rheum* 1988;31:745-9.
7. Klein RG, Hunder GG, Stanson AW, Sheps SG. Large artery involvement in giant cell (temporal) arteritis. *Ann Intern Med* 1975;83:806-12.
8. Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of temporal vessels. *Mayo Clin Proc* 1932;7:700-1.
9. Horton BT, Magath TB, Brown GE. Arteritis of the temporal vessels, previously undescribed form. *Arch Intern Med* 1934;53:400-9.

HLA-B27 and Free HLA Class I Heavy Chains in Ankylosing Spondylitis

To the Editor:

We read with interest the report from Dr. Tsai and colleagues regarding free HLA class I heavy chains in ankylosing spondylitis (AS)¹, and we believe it deserves comment. The authors found a higher expression of HLA class I free heavy chains, as defined by HC10 positivity, which reacts preferentially with epitopes of HLA-B and C alleles, on the surface of monocytes of AS patients compared with monocytes from healthy controls. In the introduction the authors correctly remind us that “free HLA class I heavy chains are rarely expressed,” but they emphasize that B27 behaves differently compared with other class I alleles because the “low affinity binding of β_2m and peptides with B27 heavy chain may shift the equilibrium to favor dissociation”. It is therefore very surprising that B27 positive AS patients have been compared with B27 negative (19 out of 21) controls and with rheumatoid arthritis patients with unknown locus B antigens (the majority were, presumably, B27 negative). The differences found in this study may therefore simply reflect the B27 positivity of the patients rather than the disease itself. Comparison with B27 positive controls is fundamental.

We also recently investigated this issue, studying free heavy chain expression on the surface of peripheral blood mononuclear cells (PBMC) in B27+ AS patients and in B27+ healthy controls^{2,3}. We were not able to find statistical differences in the 2 groups studied, but we do acknowledge that a possible role of free heavy chain in the pathogenesis of AS is intriguing and deserves further study. We also found a 5-fold higher expression of total HLA class I molecules on CD14+ cells compared to CD3+ cells, and 3-fold higher expression compared to CD20+ cells, in both patients and in healthy subjects. The finding of Tsai, *et al* of higher expression of free heavy chain in the monocyte population compared to the lymphocyte population may therefore reflect the physiologically stronger HLA molecule expression of this population of cells.

Finally, we stress that although spondyloarthropathies share common features, they include different diseases with clinical forms associated with different HLA antigens (psoriatic arthritis, for example). Therefore the results of a study performed on patients with AS should not be represented in the title as valid for all spondyloarthropathies.

ALBERTO CAULI, MD, PhD; GRAZIA DESSOLE, PhD; ALESSANDRO MATHIEU, MD, Cattedra di Reumatologia II, Università di Cagliari, Via San Giorgio 12, 09124 Cagliari, Italy. E-mail:cauli@pacs.unica.it

REFERENCES

1. Tsai WC, Chen CJ, Yen JH, et al. Free HLA class I heavy chain-carrying monocytes — a potential role in the pathogenesis of spondyloarthropathies. *J Rheumatol* 2002;29:966-72.
2. Cauli A, Dessole G, Atzeni F, et al. Ankylosing spondylitis patients express more HLA B27 molecules compared with B27+ normal controls [abstract]. *J Rheumatol* 2000;27 Suppl 59:40.
3. Cauli A, Dessole G, Fiorillo MT, et al. Increased level of HLA-B27 expression in ankylosing spondylitis patients compared with healthy HLA-B27 positive subjects: a possible further susceptibility factor for the development of disease. *Rheumatology* 2002;41:1375-9.

Dr. Tsai, *et al* reply

To the Editor:

Dr. Cauli and colleagues point out that they were not able to find statistical difference of free heavy chain expression on the surface of PBMC between B27+ AS patients and B27+ healthy controls; instead, they found higher expression of total HLA class I molecules on CD14+ cells compared to

CD3+ and CD20+ cells in both patients and controls. They speculate that our finding of higher expression of free heavy chain in the monocyte population in patients with AS may reflect the physiologically stronger HLA molecule expression of this population of cells. If their speculation were correct, we should find higher expression of free heavy chain on the surface of monocytes in every patient and in HLA-B27+ controls, but in fact we could only detect a substantial amount of free heavy chain on the surface of monocytes from patients with high erythrocyte sedimentation rate.

In contrast to their findings, CD14+ cells had higher expression of total HLA class I molecules than CD3+ cells, and lymphocytes were reported to have the highest level of class I molecules¹. A heterozygous individual expresses 6 different class I MHC molecules on the membrane of each nucleated cell. The expression of individual or total class I molecule is regulated by various cytokines and the peptides bound in the binding clefts. For example, if high affinity intracellular peptide to a particular class I molecule is available in a virus-infected cell, the expression of this particular class I trimolecular complex will be higher and more stable than other class I molecules on the same cell. Hence, the level of expression varies in different conditions. B27 antibody binding fluorescence intensities among B27+ subjects were found to be quite variable², or even absent in one report³.

Initially, we thought W6/32 (a class I trimolecular complex reactive monoclonal antibody) reactive molecules would be lower in those cells expressing higher levels of free heavy chain on the assumption that trimolecular complex might dissociate and become HC10 reactive, but we could not come to any conclusion on this because of the wide range of binding fluorescence intensities even in the same cell population.

We believe our data are clinically meaningful and also have pathophysiologic relevance that deserves further investigation.

WEN CHAN TSAI, MD, PhD; CHUNG JERN CHEN, MD; JENG HSIEN YEN, MD, PhD; HONG WEN LIU, MD, Kaohsiung Medical University, Kaohsiung, Taiwan.

REFERENCES

1. Goldsby R, Kindt TJ, Osborne BA. Major histocompatibility complex. In: Folchetti N, Tannenbaum J, Hadler GL, editors. *Kuby immunology*. New York: W.H. Freeman and Co.; 2000:173-99.
2. Chen JC, Davis BH, Bigelow NC, et al. Flow cytometric HLA-B27 typing using CD3 gating and molecules of equivalent soluble fluorochrome (MESF) quantitation. *Cytometry* 2002;26:286-92.
3. Kirveskari J, Kellner H, Wuorelam W. False-negative serological HLA-B27 typing results may be due to altered antigenic epitopes and can be detected by polymerase chain reaction. *Br J Rheumatol* 1997;36:185-9.

Cyclophosphamide Pulse Regimen in the Treatment of Alveolitis in Systemic Sclerosis

To the Editor:

We read with interest the recent article by Giacomelli, *et al*¹ regarding cyclophosphamide (CYC) treatment of alveolitis in systemic sclerosis (SSc). This prompted us to share our experience of changes in pulmonary clinicoradiophysiological variables in 11 patients with SSc with interstitial lung disease (ILD) who had similar treatment.

Twenty patients satisfying the American College of Rheumatology preliminary criteria for the classification of SSc² were evaluated. The inclusion criterion was that ILD be confirmed on high resolution computerized

tomography (HRCT). Exclusion criteria were past or concurrent history of receiving CYC or any other concomitant diseases. The study was approved by the local ethics committee. The patients were administered CYC as 6 intravenous pulses at monthly intervals: 500 mg as first and second pulses, 700 mg as third and fourth pulses, and 1000 mg as fifth and sixth pulses. Prednisolone dose was 0.5 mg/kg body weight, tapered by 5 mg every month until stopped. Severity of cough, dyspnea score (scale 0–20)³, forced vital capacity (FVC), DLCO, chest radiograph score (0–10)³, and HRCT score (0–30)⁴ were recorded at the start and after completion of 6 months of therapy. A change of more than 10% in the values from baseline was considered significant for improvement or deterioration.

The mean age of the patients was 30.36 years (range 21–52). All were women. Four had diffuse SSc and 7 had limited SSc. Duration of SSc was 5.45 ± 2.54 years. Antinuclear antibodies were positive in all, and anti-Scl70 was positive in 8 patients. Three patients had no symptoms of cough or dyspnea. Duration of pulmonary symptoms in the remaining patients was 1.35 ± 1.17 years. Raynaud's phenomenon was present in all, and 2 patients had distal extremity gangrene. Skin score⁵ was 6.91 ± 5.99. Barium swallow examination was abnormal in 5 patients. Two dimensional color echo Doppler examination was within normal limits in all patients. No patient had pulmonary hypertension. Arthralgias were present in 4 patients. No patient had renal or muscle involvement.

Changes in pulmonary variables are shown in Table 1. Deterioration in respiratory symptoms was not seen in any patient. After 6 months of treatment, cough improved in 2 (9%) patients, and dyspnea improved in 4 (36%) and stabilized in the remainder. FVC improved in 5 (45%) and stabilized in 6 (55%) patients. Mean FVC improved significantly ($p < 0.01$). DLCO improved in 4 (36%), stabilized in 2 (18%), and deteriorated in 5 (45%) patients. Mean DLCO showed an insignificant decline ($p = \text{NS}$), unlike the findings of Giacomelli, *et al*¹. Previous studies have reported either stabilization^{6,7} or improvement⁸ of DLCO. Initial chest radiograph was abnormal in 3 patients. Reticulonodular shadows varied from mild to severe in grade and extent without honeycombing or pulmonary hypertension. The radiographic findings remained unchanged in these patients and also in the 8 patients with initially normal chest radiograph. There have been variable reports of either similar findings⁸ or marked radiologic improvement in 50% of patients⁶. Mean HRCT score increased minimally. The extent of ground-glass haziness remained static in all but one patient as compared to previous studies reporting either regression or mild increase⁹. The extent of reticular shadows remained the same in all patients. Stabilization¹⁰ or increase in reticulonodular shadows¹ and honeycombing has been reported previously⁹.

Due to the small sample size, multiple regression analysis for evaluation of factors resulting in deterioration in 7 patients of either DLCO or HRCT score could not be performed, but none of these were related to the type of SSc or presence of respiratory symptoms (data not shown). The 4

Table 1. Mean (standard deviation) respiratory findings at start and after 6 months of treatment in 11 patients with SSc.

Finding	Baseline	After 6 mo
Cough present, n	4	3
Dyspnea score	3.63 (2.66)	2.36 (2.34)
FVC, % of predicted	61.24 (10.99)	68.91 (14.14)*
DLCO, % of predicted	51.62 (24.74)	44.56 (16.80)
Chest radiograph score	1.42 (2.67)	1.42 (2.67)
HRCT score	12.73 (5.92)	12.91 (5.59)

* $p < 0.05$.

patients with stable findings had a higher mean age, longer duration of SSc with shorter duration of pulmonary symptoms, a lower skin score, greater impairment of FVC and DLCO ($p < 0.05$), a higher chest radiograph score, and a higher HRCT score ($p < 0.05$).

Only 11 of 18 (55%) patients completed the therapy in our study. Two patients were lost to followup after first and fourth pulses. CYC had to be permanently discontinued due to severe intolerance in one and hematuria in another patient. Other side effects were cytopenias in 3 patients and infections such as oral candidiasis with recurrent pyoderma, pulmonary tuberculosis, *Pneumocystitis carinii*, herpes zoster, amoebiasis, and infection of toe ulcer in one patient each, oligo/amenorrhea in 2, alopecia in 2, intermittent erythematous pruritic facial rash in 3, oral ulcers in 2, and musculoskeletal pains in one patient. Mild nausea lasting 1–2 days was seen in almost all patients, although severe nausea and vomiting with giddiness necessitating emergency room observation was seen in only one patient.

Our study suggests that CYC pulse combined with moderate dose prednisolone is effective in clinical, functional, and radiological stabilization in the treatment of alveolitis in SSc, but is not without side effects and a high rate of discontinuation.

GAYATRI MITTAL, MD, Clinical Associate, Rheumatology Department; ZARIR UDWADIA, MD, Consultant Chest Physician, Pulmonary Department; VINAY R. JOSHI, MD, Consultant Rheumatologist, Rheumatology Department, PD Hinduja Hospital and MRC, Mumbai, Veer Savarkar Marg, Mahim, Mumbai 400 016, India.

Address reprint requests to Dr. Joshi. E-mail: dr_vjoshi@rediffmail.com

REFERENCES

1. Giacomelli R, Valentini G, Salsano F, et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. *J Rheumatol* 2002;29:731-6.
2. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581-90.
3. Watters LC, King TE, Schwarz MI, Waldron JA, Stanford RE, Cherniack RM. A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1986;133:97-103.
4. Warrick JH, Bhalla M, Schabel SI, Silver RM. High resolution computed tomography in early scleroderma. *J Rheumatol* 1991;18:1520-8.
5. Clements PJ, Lachenbruch PA, Cheng NG, Simmons M, Sterz M, Furst DE. Skin score: A semiquantitative measure of cutaneous involvement that improves prediction of prognosis in systemic sclerosis. *Arthritis Rheum* 1990;33:1256-63.
6. Akesson A, Scheja A, Lundin A, Wollheim FA. Improved pulmonary function in systemic sclerosis after treatment with cyclophosphamide. *Arthritis Rheum* 1994;37:729-35.
7. Silver RM, Warrick JH, Kinsella M, Staudt LS, Baumann MH, Strange C. Cyclophosphamide and low-dose prednisolone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. *J Rheumatol* 1993;20:838-44.
8. Ji JD, Lee YH, Shim JJ, Kang KH, Song GG. The effect of cyclophosphamide pulse therapy and low dose glucocorticoid on pulmonary fibrosis of patients with systemic sclerosis. *APLAR J Rheumatol* 1998;2:10-3.
9. Varai G, Earle L, Jimenez SA, Steiner RM, Varga J. A pilot study of intermittent intravenous cyclophosphamide for the treatment of systemic sclerosis associated lung disease. *J Rheumatol* 1998;25:1325-9.
10. Murlidhar R, Adya CM. A pilot study of cyclophosphamide pulses in established interstitial lung disease associated with systemic sclerosis. *J Indian Rheumatol Assoc* 1997;5:26-9.

Dr. Giacomelli, et al reply

To the Editor:

We read with interest the letter from Dr. Mittal and colleagues concerning their experience in treatment of scleroderma lung disease with cyclophosphamide (CYC). Their main conclusions are in agreement with our results¹. Indeed, after CYC treatment, scleroderma lung showed a stabilization or a limited worsening of both functions and computerized tomographic imaging. Although our 2 groups' findings were similar, some differences can be observed and possibly explained. In the study of Mittal, *et al*, the majority of patients were classified into the limited subset of the disease, in contrast to our population, in which mainly the diffuse subset was represented. Moreover, the differences in mean age and disease duration between the 2 populations show that they do not strictly overlap. Further, they used different criteria to assess significant improvement or deterioration in disease measures (a change of 10% from baseline vs our 15% of change). On this basis, the significant improvement of FVC, the only measure that changed significantly after CYC therapy in the Mittal study, may have been a result of this bias in assessment criteria. However, we observed an improvement in the ground-glass appearance in 10 out of 23 patients after 6 months of therapy. This finding was not confirmed in the Mittal study, and in our opinion could be related to the different therapeutic strategies used in the 2 studies. To achieve immunosuppression, we preferred a step-down CYC treatment in our patients, while Mittal and colleagues used a step-up approach.

Our findings were confirmed in a recent study by Pakas, *et al*². They combined intravenous pulse CYC with high doses of prednisolone, observing an improvement in clinical and radiological evolution of SSc related inflammatory lung disease with reversal of the underlying alveolitis.

Indeed, all our patients completed the study, while only 11 out of 20 did so in Mittal's series, but their statistical analysis was performed only on the patients that completed the study, inducing a clear problem in the analysis of the results that may be overcome by an intent-to-treat approach.

The main discrepancy between our work and the study by Mittal, *et al* is the prevalence of immunosuppressive related side effects, which significantly reduced the number of patients that completed their study. This evidence strongly suggests that screening to identify latent infectious disease is crucial in order to avoid serious infectious complications. Accurate patient selection is mandatory to achieve significant efficacy and to protect the patient from side effects.

ROBERTO GIACOMELLI, MD, Associate Professor of Medicine; ANTONIETTA FULMINIS, MD, Department of Internal Medicine and Public Health, University of L'Aquila; GABRIELE VALENTINI, MD, Professor of Rheumatology, Department of Clinical and Experimental Medicine, Division of Rheumatology, Second University of Naples; FELICE SALSANO, MD, Associate Professor of Immunology, Department of Clinical Medicine, Clinical Immunology and Allergology Unit, University of Rome "La Sapienza"; STEFANO BOMBARDIERI, MD, Professor of Medicine, Department of Medicine, Division of Rheumatology, University of Pisa; ARMANDO GABRIELLI, MD, Professor of Medicine, Institute of Internal Medicine and Hematology, University of Ancona; MARCO MATUCCI CERINIC, MD, Professor of Medicine, Department of Medicine, Section of Rheumatology, Division of Rheumatology, University of Florence, Florence, Italy.

REFERENCES

1. Giacomelli R, Valentini G, Salsano F, et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. *J Rheumatol* 2002;29:731-6.
2. Pakas I, Ioannidis JP, Malagari K, Skopouli FN, Moutsopoulos HM, Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. *J Rheumatol* 2002;29:298-304.



Consistency for Childhood Arthritis

To the Editor:

I read with interest the recent editorial, "The Place of Juvenile Onset Spondyloarthritis in the Durban 1997 ILAR Classification Criteria of JIA". *The Journal* previously published proposals for the development of classification criteria for the idiopathic arthritides of childhood in 1995 (Santiago)², and the revision of proposals for classification of juvenile idiopathic arthritis (JIA) from Durban in 1998³.

In the Durban (1997) classification of JIA there are, as summarized in the editorial, 7 subgroups that may be clinically identifiable after 6 months of disease: (1) Systemic arthritis; (2) oligoarthritis; (3) polyarthritis (rheumatoid factor negative); (4) polyarthritis (rheumatoid factor positive); (5) enthesitis related arthritis; (6) psoriatic arthritis; and (7) other arthritis.

Within the discussion the term JIA is used¹, and in addition in the original article defining the Durban criteria³, there is specific reference to "juvenile rheumatoid arthritis" and "juvenile chronic arthritis" as being terms that were major sources of disagreement in the past and which were therefore discarded in favor of the umbrella term "juvenile idiopathic arthritis." The signatories to this revision included respected practitioners in the field of pediatric rheumatology from Canada, the UK, the USA, South Africa, Australia, South America, Central America, and Europe (France). It is accepted that this classification is by no means perfect and does present difficulties in some areas such as the definitive diagnosis of psoriatic arthritis.

In the same issue of *The Journal*, there is an article⁴ entitled "Preliminary Definition of Disease Flare in Juvenile Rheumatoid Arthritis." The first sentence reads, "Juvenile rheumatoid arthritis (JRA) is a group of inflammatory autoimmune conditions of childhood..." There are 3 key references (numbers 3,4, and 5) that use the term "juvenile rheumatoid arthritis" or "JRA."

The next article in that issue is entitled "Osteopenia in Adults with a History of Juvenile Rheumatoid Arthritis"⁵, and another is "Differences in the Profiles of Circulating Levels of sTNFR and IL-1 Receptor Antagonist Reflect the Heterogeneity of the Subgroups of Juvenile Rheumatoid Arthritis"⁶.

It is disappointing that on page 1079 there is yet another article, "Higher Response rate in the Phase I/II Study of Meloxicam in Juvenile Rheumatoid Arthritis"⁷, which includes among its authors the first author of the Editorial on JIA.

There are therefore no less than 4 articles in that May 2002 edition of *The Journal* that use the term "juvenile rheumatoid arthritis" as a generic term in the title.

Given that *The Journal* has seen fit not only to publish the original and revised classification criteria^{2,3}, and in addition an Editorial in which aspects of the classification are discussed and where the generic term used is clearly "juvenile idiopathic arthritis," it seems inconsistent to include 4 other articles in the same edition that refer to juvenile arthritis in all its forms and allow them to be described as "juvenile rheumatoid arthritis."

Surely the time has come for an international publication of the standing and reputation of *The Journal of Rheumatology* to take an initiative and a lead in promoting the unification of the concepts and terminology of "juvenile idiopathic arthritis" and to clarify and refine the use of the term "juvenile rheumatoid arthritis."

To many practising pediatric rheumatologists, "juvenile rheumatoid

arthritis" refers only to polyarticular arthritis that is rheumatoid factor positive, i.e., group 4 of the revised Durban classification³, and that typically presents in girls in their second decade of life and then evolves into an adult form of RA. In many respects this subgroup could be redefined as "true JRA." This subgroup 4 is further refined, as are all the groups in the Durban classification, in terms of definition, exclusions, and descriptors.

The Journal is in a prime position through the editorial process to effect changes in the use of the term "juvenile rheumatoid arthritis" as a generic term for what is known worldwide as "juvenile idiopathic arthritis" or "juvenile arthritis" or what used to be termed "juvenile chronic arthritis."

While there may be other nonmedical factors that contribute to the continued use of "rheumatoid" as the generic term in the USA, these surely should not stand in the way of standardization.

I would therefore suggest that the Editorial Board should insist that the term "juvenile rheumatoid arthritis" should not be acceptable as a generic term for publications relating to arthritis in children in general.

Many pediatric rheumatologists are of the opinion that the term "juvenile rheumatoid arthritis" should be avoided for the following reasons: (1) The term "rheumatoid" is very evocative and for many parents the use of this term may immediately conjure up a spectre of a very severely affected adult with advanced severe disease. (2) It is inaccurate in terms of the Durban classification. (3) There is some indication that the use of the term "rheumatoid" in insurance applications may result in loading of premiums even though the adult may merely have had oligoarthritis, which was managed with one intraarticular injection that effected a significant improvement, and there was no further disease activity.

I do not understand therefore how the Editorial Board of *The Journal* can allow this inconsistency to continue to permeate its pages. However, it seems as if old conventions are ingrained, as the publicity for the next eagerly anticipated major international pediatric rheumatology conference, "Pediatric Rheumatology 2003: Park City and Beyond," which is promoted by the American Academy of Pediatrics, Section on Rheumatology, is using the term "juvenile rheumatoid arthritis"⁸.

JOHN A. SILLS, MA, MB, BChir, FRCP, FRCPCH, DCH, Consultant Paediatric Rheumatologist, Royal Liverpool Children's Hospital, Liverpool L12 2AP, UK. E-mail: John.sills@rlch-tr.nwest.nhs.uk

REFERENCES

1. Burgos-Vargas R, Rudwaleit M, Sieper J. The place of juvenile onset spondyloarthropathies in the Durban 1997 ILAR Classification Criteria of juvenile idiopathic arthritis. *J Rheumatol* 2002;29:869-4.
2. Fink CM and the Task Force for Classification Criteria. Proposal for the development of classification criteria for idiopathic arthritides of childhood. *J Rheumatol* 1995;22:1566-9.
3. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol* 1998;25:1991-4.
4. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. *J Rheumatol* 2002;29:1058-64.
5. French AR, Mason T, Nelson AM, et al. Osteopenia in adults with a history of juvenile rheumatoid arthritis. *J Rheumatol* 2002; 29:1065-70.
6. Muzaffer MA, Dayer J-M, Feldman BM, et al. Differences in the profiles of circulating levels of soluble tumor necrosis factor receptors and interleukin 1 receptor antagonist reflect the heterogeneity of the subgroups of juvenile rheumatoid arthritis. *J Rheumatol* 2002;29:1071-8.
7. Foeldvari I, Burgos-Vargas R, Thon A, Tuerck D. High response rate in the phase I/II study of meloxicam in juvenile rheumatoid arthritis. *J Rheumatol* 2002;29:1079-83.
8. American Academy of Pediatrics. Pediatric Rheumatology 2003: Park City and Beyond. [Cited January 24, 2003] www.aap.org/profed/03rheum.pdf

Neck and Upper Limb Pain

To the Editor:

In a recent interesting study Van der Windt, *et al*¹ described a relationship between extent of pain in the neck–upper limb area and psychological distress. Patients with generalized pain had significantly higher scores, particularly for depression, on the Hospital Anxiety and Depression Scale¹ versus subjects with localized pain. At issue then is why subjects with generalized pain should be more depressed than subjects with localized pain?

Part of the answer to this problem relates to findings of 2 recent reviews on the relationship between pain and depression. In the first evidence based structured review (not a metaanalysis), Fishbain, *et al*² showed that: (1) depression is more common in patients with chronic pain than controls; (2) the preponderance of the evidence indicated that depression followed the development of chronic pain; (3) however, depression predisposition predisposed to the development of depression following the development of chronic pain; and (4) most important, there was a relationship between the perceived severity and frequency of pain and development of depression. This last study was recently supported by a metaanalysis performed on studies utilizing patients with rheumatoid arthritis (RA) who were depressed and had pain³. Here, effect sizes for depression were shown to vary in a linear manner in proportion to the effect size for pain. The authors concluded that depression is more common in patients with RA than in healthy individuals, due in part to the levels of pain experienced³. Thus pain severity can be related to the development of depression^{2,3}. It is to be noted that Windt, *et al*¹ found that their generalized pain subjects had significantly greater levels of pain than those with localized pain¹. Thus, these findings would indirectly support the conclusions of the above reviews^{2,3}. In addition, it is to be noted that 2 previous studies^{4,5} have also found an association between pains (multiple pains) and depression.

DAVID A. FISHBAIN, MD, FAPA, Professor of Psychiatry, Neurosurgery and Anesthesiology, University of Miami School of Medicine, and University of Miami Comprehensive Pain and Rehabilitation Center, Miami, Florida, USA.

REFERENCES

1. Van der Windt D, Croft P, Penninx B. Neck and upper limb pain: more pain is associated with psychological distress and consultation rate in primary care. *J Rheumatol* 2002;29:564-9.
2. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain* 1997;13:116-37.
3. Dickens C, McGowan L, Clark-Carter B, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with a meta-analysis. *Psychosom Med* 2000;64:52-60.
4. Benjamin S, Morris S, McBeth J, et al. The associations between chronic widespread pain and mental disorder. *Arthritis Rheum* 2000;43:561-7.
5. Dworkin SF, Von Korff M, LeResche L. Multiple pains and psychiatric disturbance: An epidemiologic investigation. *Arch Gen Psychiatry* 1990;47:239-44.

Fluvoxamine Therapy for Fibromyalgia

To the Editor:

Pain in patients with fibromyalgia (FM) is difficult to treat, and no single intervention has been universally accepted. Fluvoxamine (FL), a selective serotonin reuptake inhibitor (SSRI), has been used for patients with depressive illness and obsessive-compulsive disorders¹. Since patients with FM often have mild depression/depressive state² or obsessive-compulsive personality disorders, it is reasonable to study FL as a treatment for FM. We

Table 1. Demographic background of patients with fibromyalgia (FM).

	Fluvoxamine Group	Amitriptyline Group
No. of patients available at start	38	30
No. of withdrawals	6	12
Due to side effects	5	6
Discontinued attending hospital	1	6
Side effects		
Nausea	6	0
Palpitation	1	0
Drowsiness	0	4
Epigastralgia	1	1
Dizziness	0	1
Fatigue	0	1
Thirst	0	1
No. of patients remaining	32	18
Mean age, yrs	45.3	39.1
Ratio male/female	4/26	4/14
Ratio, primary to secondary FM	22/8	15/3
Disease duration, yrs	3.3	3.7
No. of tender points at start	13.5	13.9

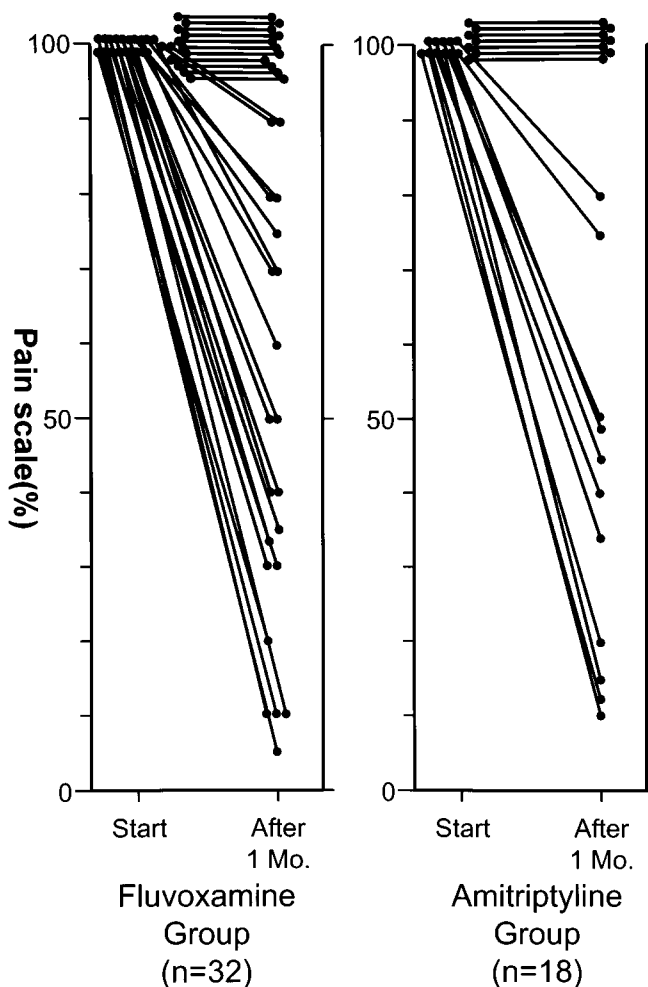


Figure 1. Visual analog scale profiles after treatment for “widespread pain” in each fibromyalgia patient group.

describe for the first time a beneficial result of FL therapy for pain in patients with FM.

Sixty-eight Japanese patients with FM were enrolled between 1991 and 2001; all were diagnosed by the American College of Rheumatology 1990 criteria. These patients were divided into 2 groups: 30 patients who were treated with amitriptyline (AM) (mean dose 20 mg/day) and 38 patients with FL (mean dose 25 mg/day). Effectiveness for pain was evaluated by a visual analog scale (VAS) 4 weeks after starting medication. AM or FL was evaluated as effective only when a patient reported that pain decreased by $\geq 50\%$.

Twelve (40%) patients treated with AM and 6 (16%) treated with FL dropped out of the study because of side effects or other reasons. For the remaining respective 18 and 32 patients, mean age, male to female ratio, ratio of primary to secondary FM, disease duration, and number of tender points were not significantly different (Table 1). Side effects in the AM group were drowsiness in 4, and epigastralgia, hypersomnia, dizziness, fatigue, and thirst in one patient each. Adverse effects in the FL group were nausea in 6, and palpitation, constipation, and epigastralgia in one patient each.

Nine (50%) patients of the AM group and 13 (41%) patients of the FL group in the respective groups reported effective pain relief at 4 weeks after medication, and these frequencies did not differ statistically (chi square = 0.411, $p = 0.5647$). The actual VAS values in each patient and in each group are shown in Figure 1.

Efficacy of AM for pain in FM patients has been established through multiple double-blind controlled studies³. Since FL in relatively low doses was effective for pain in 41% of FM patients, a frequency not different from AM-treated patients, it is likely that FL will be useful for some patients with FM.

MASAHIKO NISHIKAI, MD; KUMIKO AKIYA, MD, Department of Internal Medicine, National Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan.

REFERENCES

1. Hollander E. Treatment of obsessive-compulsive spectrum disorders with SSRIs. *Br J Psychiatry* 1998;173:7-12.
2. Nishikai M. Fibromyalgia in Japanese. *J Rheumatol* 1992;19:110-4.
3. Crette S, McCain GA, Bell DA, et al. Evaluation of amitriptyline in primary fibrositis. A double-blind, placebo-controlled study. *Arthritis Rheum* 1986;29:655-9.

Salicin and Treatment of Rheumatic Diseases

To the Editor:

Buchanan and Kean¹ presented an account of "The Treatment of Acute Rheumatism by Salicin, by T.J. Maclagan — The Lancet, 1876." Unfortunately, the authors seemed to be unaware of the apothecaries' units of mass used in the report of Maclagan. Maclagan² administered to his patient 12 *grains* (equivalent to a total of 778 milligram) salicin every 3 hours, which Buchanan and Kean mistook for 12 *gram* (g) every 3 hours. Salicin is *in vivo* metabolized to salicylic acid³. The administration of 12 g of salicin would be equivalent to the administration of 5.8 g of salicylic acid every 3 hours, which would have led almost certainly to toxic symptoms. Buchanan and Kean¹ also mention a recently published trial⁴ in which, as they say, "salicin has proven better than placebo for low back pain". However, this trial was conducted with willow bark extract, which cannot be equated with salicin. Salicin is just one, although probably the best known, constituent of willow bark extract⁵. Pharmacokinetic studies indicate that the clinical efficacy of willow bark extract cannot be attributed to salicin alone³, since therapeutic doses of willow bark extract lead to much lower serum salicylate concentrations than observed after analgesic doses of synthetic salicylates.

IRMELA WAGNER, M^{Pharm}; LUTZ HEIDE, Ph^D, Pharmaceutical Institute, Tübingen University, Tübingen, Germany.
E-mail: heide@uni-tuebingen.de

REFERENCES

1. Buchanan WW, Kean WF. The treatment of acute rheumatism by salicin, by T.J. Maclagan — The Lancet, 1876. *J Rheumatol* 2002;29:1321-3.
2. Maclagan TJ. The treatment of acute rheumatism by salicin. *Lancet* 1876;I:342-3.
3. Schmid B, Kotter I, Heide L. Pharmacokinetics of salicin after oral administration of a standardised willow bark extract. *Eur J Clin Pharmacol* 2001;57:387-91.
4. Chrusasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conrad C. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* 2000;109:9-14.
5. European Scientific Cooperative on Phytotherapy. Salicin cortex – Willow bark. In: ESCOP Monographs on the Medicinal Uses of Plant Drugs; Fascicule 4. Exeter, UK: European Scientific Cooperative on Phytotherapy; 1997.

Correction

Miller LE, Grifka J, Schölmerich J, Straub RH. Norepinephrine from synovial tyrosine hydroxylase positive cells is a strong indicator of synovial inflammation in rheumatoid arthritis. *J Rheumatol* 2002;29:427-35. The area of a field of view at 400 \times magnification was calculated incorrectly. The stated densities of the histological measures should be divided by 6.2 to calculate the correct number of structures per mm². The densities of macrophages, T cells, tyrosine hydroxylase positive cells, and collagen IV positive blood vessels were incorrect. The results and conclusions of the study are not affected by this mathematical miscalculation. We regret the error.