ARTHRITIS & RHEUMATISM
Vol. 48, No. 5, May 2003, pp 1461–1470

LETTERS

DOI 10.1002/art.10966

Genetic linkage of primary hip osteoarthritis with restricted areas on chromosome 11q: comment on the article by Chapman et al

To the Editor:

In a recent article (1), Chapman et al described a genetic linkage of primary hip osteoarthritis (OA) with restricted areas on chromosome 11q. This is an elegant study, which may well provide important new insights into hip OA. Nonetheless, I would like to raise concerns about their choice of patients for this study.

Their cohort, as described previously (2), was ascertained by identifying siblings of patients in the UK who had undergone total hip replacement for primary hip OA. The authors went to considerable lengths to make sure that primary OA was the reason for the joint damage. There are, however, at least two other factors that may need to be taken into account. First, by choosing patients who underwent total hip replacement, they are, by definition, choosing patients with advanced disease. There is some evidence to suggest that a different set of factors may be involved in the incidence and progression of knee OA (3,4). If this is the case for hip OA as well, then a study of this sort may identify genes involved in disease progression rather than disease initiation, although it would be impossible to differentiate between the two without investigating other groups of patients.

Another important consideration is health services utilization. Not everyone in the UK with advanced OA undergoes joint replacement surgery. Some patients with advanced OA suffer relatively little, others do not seek help in spite of severe symptoms, and others refuse surgery for one reason or another (such as comorbidity or obesity) (5,6). It is possible, therefore, that the genes identified in this study will be markers of some factor that predisposes persons with hip OA to require joint replacement surgery, rather than being markers of disease.

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DOI 10.1002/art.11064

Reply

To the Editor:

Dieppe is quite right that we chose our patient cohort to contain those with advanced disease, as ascertained by total joint replacement of the hip for primary OA. This was a conscious decision that was made at the inception of our project and ensured that we studied individuals in whom the diagnosis of severe symptomatic OA was not in doubt. In complex traits, a more severe phenotype frequently has a stronger genetic component, and we were confident that this strategy would increase our likelihood of studying patients in whom genetic susceptibility was a major risk factor. Indeed, subsequent epidemiologic studies have demonstrated an increased genetic risk in those individuals whose disease has necessitated joint replacement (1). Our decision to focus on severe disease would therefore be considered very sensible by any molecular geneticist attempting to map susceptibility genes for a common complex disease. In addition, our use of joint replacement also enabled us to study an aspect of the disease that has a high economic burden. Interestingly, other investigators are now turning to joint replacement in their genetic studies of large-joint OA (2).

As yet, no data suggest that different genes are involved in the initiation and progression of hip OA. If this is the case, we can see no reason why our ascertainment could not be used to identify genes involved in both.

We accept that some persons with severe hip OA do not undergo hip replacement surgery. However, the perception that hip replacement is very successful at relieving symptoms and restoring function is widespread in the UK population, and we believe it likely, therefore, that our cohort of patients with hip OA is a representative population. Furthermore, this cohort matched the normal population in factors such as obesity (3). Overall, it strikes us as most unlikely that individuals with severe hip disease who merit but do not then undergo surgery can be genetically distinct from those with severe disease who do undergo surgery.

It is clear from published genetics studies that 2 different clinical strategies are being used to recruit individuals with large-joint OA: end-stage symptomatic disease characterized by the need for joint replacement surgery, and radiographically assessed disease that may or may not be symptomatic or progressive. Which strategy is important, and which is currently yielding the most promising genetic data? We would argue that it is the former in both cases.

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DOI 10.1002/art.11066

Increased mortality in early inflammatory polyarthritis: comment on the article by Goodson et al

To the Editor:

We read with interest the recent article by Goodson et al (1). The authors report that increased cardiovascular mortality occurred in patients with seropositive inflammatory polyarthritis (IP), while no increased mortality was observed in patients with rheumatoid arthritis (RA). In their discussion, the authors highlight a possible connection between systemic inflammatory conditions, rheumatoid factor (RF), and atherosclerosis.

We have several problems with these results. The authors disregard the presence of neoplasm, which was the second largest cause of death in the study group (23.1% of women and 33.3% of men). It is well known that the presence of RF is associated with diseases other than RA (e.g., infectious disease and neoplasms). It is common practice to consider malignancy in an elderly patient (>60 years of age) who presents with seropositive polyarthritis. The increased mortality observed in the seropositive group is therefore not very surprising, because patients with paraneoplastic arthritis were not excluded. Several other studies, in which such patients were excluded, failed to demonstrate a correlation between mortality and the presence of the RF in patients with RA, indicating that RF may be linked more to malignancy than to inflammation (2–5). Furthermore, the authors' definition of IP ("swelling of at least 2 joints that had persisted for at least 4 weeks") is not very consistent. As shown in Table 1, the entire IP cohort had a median of 3 swollen and tender joints (range 0–8), making us understand that some of the patients did not have arthritis. The duration of arthritis in the study group was 4 weeks, even though the authors state they used American College of Rheumatology criteria at baseline, for which the time span is 6 weeks.

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DOI 10.1002/art.11067

Reply

To the Editor:

We thank Slettjord and Nossent for their interest in our study. Although cancer accounted for 23% and 33% of all deaths in female and male patients, respectively, these proportions reflect national mortality patterns and do not represent an increase over expectations in the general population. Such an absence of increased mortality from cancer has been shown in several other large studies (1–3). We do not find it credible that unrecognized paraneoplastic syndrome was the underlying explanation for arthritis in those subjects who died of cancer. First, as stated above, the number of cancer deaths was not increased, and second, the median interval between arthritis onset and cancer death was 4.6 years (interquartile range 2.8–4.8 years).

Slettjord and Nossent also refer to our definition of IP but have misinterpreted our findings. The inclusion criterion was joint swelling for at least 4 weeks prior to entry, as determined by the referring physician. Thus, it is not surprising that in the short interval before the baseline assessment a few patients, either because of therapy or due to natural remission, had no active joints at that time.

Finally, although we applied the American College of Rheumatology criteria at several points during followup of these subjects, despite the problems with this (4,5), we have always made clear our consistent approach to defining inflammatory polyarthritis in the Norfolk Arthritis Register as swelling persisting for at least 4 weeks.

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DOI 10.1002/art.10971

High-dose cyclophosphamide therapy without stem cell rescue for severe refractory autoimmune illnesses: comment on the article by Moore et al

To the Editor:

We read with interest the recent article by Moore et al (1) comparing CD34-selected versus unmanipulated hemopoietic stem cell transplantation (HSCT) for severe, refractory rheumatoid arthritis. The study design intended to examine whether T cell depletion confers additional benefit in the HSCT procedure due to the theoretical possibility of reinfusing autoreactive T cells at the time of stem cell rescue. Clearly, they, as we, are disappointed with the long-term results of peripheral blood stem cell transplantation for the treatment of severe and refractory autoimmune diseases.

We have been studying the same dose of cyclophosphamide used by Moore et al, but without stem cell rescue. Brodsky et al (2) were the first investigators to show that high concentrations of aldehyde dehydrogenase in the pleuripotent stem cell protect against the cytotoxic effects of cyclophosphamide, thus allowing for full and spontaneous marrow recovery. This obviates the need for stem cell rescue and eliminates the possibility of reinfusion of any pathogenic autoreactive T cells. Importantly, B and T cells have no inherent protection against the cytotoxic effects of cyclophosphamide. We recently reported 2 patient populations treated in this manner, one with severe refractory systemic lupus erythematosus (3) and one with severe refractory chronic inflammatory demyelinating polyneuropathy (4) (a B and T cell–mediated autoimmune neuropathy).

Our patients experienced a median of 9.5 days (range 6–15 days) of neutropenia. In comparison, Moore et al report neutropenia for a median of 13.5 days (range 9–21 days) in the unmanipulated cohort and 14 days (range 11–24 days) in the manipulated cohort. It is unclear at this time why infusion of stem cells increased the duration of neutropenia in the unmanipulated cohort. It is possible that the infusion of T cells has a deleterious effect on marrow recovery.

Moreover, in our series, with a median followup of 660 days (range 330–1,200 days), no patient experienced disease progression, and all patients continue to exhibit a major response, with several patients in a complete remission. In the cohort described by Moore et al, the median time to disease recurrence was 147 days in the CD34-selected group and 201 days in the unmanipulated-cell group. We find it plausible that an infusion of 5×10^4 T cells/kg remains a high enough T cell burden to allow for disease reintroduction at the time of stem cell rescue.

Last, 200 mg/kg of cyclophosphamide without stem cell rescue eliminates the cost for stem cell mobilization, leukapheresis, stem cell cryopreservation, and graft manipulation and may be associated with a better clinical outcome. Therefore, we suggest that a nontransplant cohort be incorporated in future high-dose chemotherapy trials for severe autoimmune illnesses.

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DOI 10.1002/art.10982

CD34-selected versus unmanipulated grafts for severe rheumatoid arthritis: comment on the article by Moore et al

To the Editor:

We read with interest the recent report by Moore et al (1) regarding a randomized trial in patients with severe rheumatoid arthritis (RA), comparing CD34-selected and unmanipulated hemopoietic stem cell transplantation after conditioning with high-dose cyclophosphamide. The results of the study are consistent with previous case reports and phase I/II studies demonstrating the feasibility, safety, and efficacy of this novel treatment strategy. Relapses and treatment failures have also been observed. These have been ascribed to insufficient T cell depletion of the host and/or the graft, based on the importance of in vivo T cell depletion in the conditioning regimen in rodent arthritis models (2). The authors concluded that ex vivo T cell depletion of the graft after this particular conditioning regimen has no benefit, contending the validity of the European Group for Blood and Marrow Transplantation/European League Against Rheumatism recommendation on graft manipulation.

We believe that the design of the study, including the treatment arms chosen, does not allow definitive conclusions regarding the therapeutic value of T cell depletion. First, CD34

cell selection as a means to achieve T cell depletion depletes not only CD19 and CD8 cells, as mentioned by Moore et al, but also monocytes. Monocytes are abundantly present in peripheral blood stem cell grafts and have been shown to exert immunosuppressive effects on T cells in vitro (3,4). The outcomes in the 2 study groups may therefore actually reflect true (unintended) immunomodulation by infusing an immunologically altered stem cell product.

Second, the level of T cell depletion by CD34 selection of the graft (median number of CD4 + CD8 cells, 0.08×10^6/kg) may have been insufficient. The importance of intensive T cell depletion of the graft was borne out by early studies on allogeneic stem cell transplantation for hematologic malignancies. These showed an unexpected increase in the incidence and severity of acute graft-versus-host disease (GVHD) with CD34-selected but suboptimally T-depleted grafts (5). Subsequent studies demonstrated that in the CD34-selected setting, acute GVHD could be effectively prevented as long as T cell depletion was adequate, i.e., the number of infused T cells was $< 0.05 \times 10^6$/kg (6).

Third, recent studies on intensive immunosuppression and autologous (manipulated) stem cell transplantation in RA have shown marked changes in synovial tissue T cell infiltrates, but not other cell types, in samples obtained pre- and post-transplantation, which accompanied fluctuations of disease activity (7,8). These results are consistent with data in experimental animal models of autoimmune disease and lend support to the view that additional in vivo T cell depletion might improve the clinical efficacy of stem cell grafting. Indeed, a durable response was observed in a patient with RA who was receiving a myeloablative transplant regimen comprising both in vivo T cell depletion of the host and ex vivo manipulation of the graft (9).

Whether larger randomized studies on CD34-selected versus unmanipulated grafts, as referred to by the authors, should be pursued is therefore a matter of debate, because such studies will not address the pivotal question of the importance of T cell depletion of the host.

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DOI 10.1002/art.11071

Reply

To the Editor:

We thank the editor for the opportunity to respond to the comments by Prestrud et al and van Laar and Pavletic. Regarding the letter by Prestrud and colleagues, we are aware of the study by Brodsky et al (1) using cyclophosphamide, 200 mg/kg, without stem cell rescue in patients with autoimmune diseases. However, it is important to note that only 2 of the patients in the published series had rheumatoid arthritis (RA). Both patients had Felty's syndrome, and the procedure was performed for severe neutropenia, not rheumatoid disease. Even though both patients were receiving granulocyte colony-stimulating factor (G-CSF) prior to and after high-dose cyclophosphamide therapy, the median time to neutropenia was still 17 days. Because followup of these patients is incomplete, the duration of their response is unclear, and it is difficult to compare their response with that of patients in our study, who had resistant disease.

It is now well established in all published case series of HSCT in RA that disease recurrence is common (2–4). It is unclear whether recurrence of disease is attributable to reinfusion of pathogenic cells in the stem cell graft or to residual autoreactive cells remaining in the host after treatment with cyclophosphamide. Given that cyclophosphamide is not myeloblative, it is possible that the stem cell itself needs to be eradicated or replaced to prevent recurrence; however, this may increase the morbidity of the procedure.

Recurrence of disease following HSCT may be disease specific. Recurrence appears to be more common in patients with RA than in patients with other autoimmune diseases, such as systemic lupus erythematosus (SLE). Patients with SLE appear to experience sustained improvement in disease activity (with followup of >3 years), suggesting that the disease is very sensitive to high doses of cyclophosphamide, irrespective of whether stem cells are reinfused (5) or not (1). Although we appreciate that cyclophosphamide without stem cell rescue

may be efficacious in some diseases, we believe that it is not valid to compare case series of patients with SLE and chronic inflammatory demyelinating polyneuropathy with those of patients with RA, which is clearly a different disease with possibly a different sensitivity to cyclophosphamide.

As Prestrud et al point out, our primary hypothesis was to examine whether T cell depletion of the graft would lead to a better outcome of HSCT in patients with RA. As discussed in our article, there was no difference between the study arms in terms of outcome, and, in fact, there was a trend toward a worse outcome in the CD34-selected cohort. Thus, it is unclear why Prestrud et al would argue for even further T cell depletion, which not only may be less effective but also may increase the likelihood of infection. Both Verburg et al (2) and Bingham et al (3) have reported case series of patients with RA in which a lower T cell content of the graft was used, with results similar to ours, suggesting that T cell depletion of the graft is not the answer to improving outcomes.

In the hematology literature, the duration of neutropenia is expressed by convention, as the number of days from stem cell infusion until a neutrophil count $>0.5 \times 10^9$/liter is attained for 3 consecutive days. This may not be the same as the number of days of neutropenia, which by definition is always less because of the delayed effect of cyclophosphamide. Thus, we would argue that the comparison made by Prestrud et al regarding our neutrophil engraftment and the number of days of neutropenia in their study is not appropriate. We also note that all case series using cyclophosphamide without stem cell rescue use G-CSF, which may shorten the length of neutropenia but may also increase cost significantly. Patients in our study did not receive G-CSF routinely.

Although the results of therapy using high-dose cyclophosphamide without stem cell rescue are interesting and warrant further study, the possible increased rate of infection associated with prolonged neutropenia may limit its use. It is the objective of most physicians working in this area to care for their patients safely and effectively, in accordance with the European Group for Blood and Marrow Transplantation/European League Against Rheumatism guidelines (EBMT/EULAR) (6). We would like to point out that the initial results of our trial were superior to those of most published therapies in RA, but it is maintaining long-term responses that will be the goal of future research in the field of HSCT for autoimmune diseases.

Regarding the letter by van Laar and Pavletic, in general we agree that the issue of T cell depletion of the graft in HSCT for autoimmune diseases remains unresolved. We would argue, however, that it is T cell depletion of the host that may be more important. This concept is supported by studies in the rodent arthritis model, which demonstrated that more intensive conditioning, aimed at ablating autoreactive cells, correlated with better responses (7). In the human setting, however, use of irradiation and more intensive conditioning may increase toxicity, making confirmation of the animal studies difficult.

Although use of a myeloblative regimen has resulted in a significant response in one patient (8), it should be noted that the only patient with RA who has died because of a stem cell transplant received the same conditioning (Tyndall A: personal communication). Chemotherapy or immunosuppression is unlikely to eradicate autoreactive cells in the patient, and it is possible that the only way to achieve this goal is to use an allogeneic graft, which allows a graft-versus-host lymphocyte reaction. Patients who have received allogeneic transplants for coexistent malignancies have demonstrated prolonged remissions, confirming this hypothesis (9). Use of an allogeneic transplant, however, is currently not a realistic option, because it is associated with higher morbidity and mortality compared with autologous transplantation.

Definitive conclusions about T cell depletion of the graft cannot be made based on our trial. However, because of the difficulty in recruiting patients into HSCT trials, this study remains the only published randomized trial in the field of HSCT in autoimmune diseases and therefore provides data from which further studies can be designed. The EBMT/EULAR guidelines for T cell depletion (6) are not based on any human trial data but on a rodent arthritis model described by Knaan-Shanzer et al (10). This study did not employ T cell depletion of the rodent arthritis marrow due to technical difficulties. Recommendations for T cell depletion are based solely on the fact that rat bone marrow contains $\log_1$ fewer T cells compared with human marrow (7).

Van Laar and Pavletic argue that the T cell depletion in our study may not be sufficient. As mentioned above, studies by Verburg et al (2) and Bingham et al (3), using more intensive T cell depletion, had results similar to those in our study, which suggests that further depletion of T cells is not the answer to maintaining responses. We believe that the threshold of 0.05×10^6 T cells/kg in the allogeneic setting is not applicable to the autologous setting in autoimmune diseases and therefore cannot be used as a reliable guide.

We did note that monocytes were also depleted by the CD34 selection process. However, there was no difference in the cytokine profile of monocytes in either arm of the study (Moore J: unpublished observations), suggesting that there was no unintended immunomodulation. A recent observation by Bingham et al (11), that memory T cell infiltration into the synovium was associated with recurrence, is important; unfortunately, it is unclear whether these cells were from the graft or were those remaining in the host after conditioning. Gene marking studies may provide the answer to this question, thus providing data on the rational use of T cell depletion of the graft, which we believe to be an expensive and unproven therapy in the setting of HSCT for patients with RA.

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DOI 10.1002/art.10967

Efficacy of low-dose versus high-dose cyclophosphamide in lupus nephritis: comment on the article by Houssiau et al

To the Editor:

In a recent article, Houssiau et al purport to provide evidence that low-dose cyclophosphamide therapy is effective treatment for lupus nephritis, and that low-dose therapy had therapeutic results comparable to those of high-dose therapy, while causing less toxicity. (Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido E, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31).

The authors note that in their study, the probability of treatment failure in the low-dose cohort was not statistically significantly different from that in the high-dose cohort, and that there were fewer severe adverse effects in the low-dose group, although this was also not statistically significant. Although this statement is technically correct, the implication drawn from the conclusion is flawed and represents a misinterpretation of Type II statistical error. The study is declared to be powered at only 22% to detect a meaningful difference at the 0.05 level. Under such circumstances, a negative result is uninterpretable, because there is at least a 78% chance that a very real difference would have been missed by the authors because of the small size of their sample, and there is concomitantly low confidence that the treatment regimens were indeed therapeutically equivalent.

Moreover, while it is unlikely that the authors prospectively designed their study to be powered at the 22% level to detect differences, there is no comment in the article stating what the original enrollment plans were, how the prospective design was influenced by the presumed failure to complete the target enrollment, or what the possible biases were that may have been introduced by the failure to enroll a complete cohort. A more appropriate conclusion to be drawn from these data would be that the utility of low-dose cyclophosphamide is unclear, but that the apparently encouraging results obtained in this incomplete trial suggest that a definitive evaluation should be performed.

The impression left by Houssiau and colleagues (an impression that is encouraged by the accompanying editorial) is that there are data to suggest equivalency of low-dose and high-dose cyclophosphamide therapy in lupus nephritis. When published in a premier journal, this conclusion may have a potent impact on practice patterns worldwide; in fact, I have already heard this article cited as evidence that patients should be treated with a low-dose regimen to minimize toxicity while not sacrificing efficacy. Although low-dose cyclophosphamide therapy may or may not be equivalent to high-dose therapy, failure to detect a difference in an underpowered study hardly provides a compelling reason to change practice patterns. Pending the results of a larger study, care should be taken to ensure adequate treatment of patients with lupus nephritis.

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DOI 10.1002/art.11065

Reply

To the Editor:

Block's comments on the results of the Euro-Lupus Nephritis Trial are correct from a statistical point of view. Statistical power should, however, be balanced with feasibility.

When the Euro-Lupus Nephritis Trial was designed in 1994, we decided to randomize 90 patients into the study, which was a reasonable goal given the rarity of lupus nephritis, the strict inclusion/exclusion criteria, the need for very long followup, and the absence of any logistic or financial support from pharmaceutical companies. In this respect, it should be stressed that all randomized trials in systemic lupus erythematosus published in the past 5 years had fewer patients (Ruiz-Irastorza G, Khamashta MA, Castellino G, Hughes GR. Systemic lupus erythematosus. Lancet 2001;357:1027–32). We knew beforehand that our study would be underpowered because we were unable to gather the very large number of

patients needed for an equivalence trial. Yet, we decided to run the study and managed to complete the original target enrollment. Contrary to what Block implies, we did not change our initial plans.

Interestingly, the elegant preliminary study on mycophenolate mofetil in lupus nephritis by Chan et al, published in a premier journal (Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al, Hong Kong-Guangzhou Nephrology Study Group. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. N Engl J Med 2000;343:1156–62), also lacks statistical power. Nonetheless, that trial is important and might influence our future clinical practice. It has certainly been a stimulus to further studies.

Whether the results of the Euro-Lupus Nephritis Trial will have an impact on clinical practice is currently unknown. We presented several caveats in the discussion of our article and have been cautious in our conclusions. We share Block's view that adequate treatment should be ensured for patients with lupus nephritis. Therapeutic goals have evolved over the past 2 decades and now include not only preservation of kidney function but also avoidance of adverse effects and preservation of quality of life (including fertility issues). These objectives will remain the responsibility of the clinicians faced with meeting patients' expectations.

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DOI 10.1002/art.10937

Persistent efficacy of tumor necrosis factor α blockage therapy in SAPHO syndrome: comment on the article by Wagner et al

To the Editor:

The report by Wagner et al dealing with the efficacy of tumor necrosis factor α (TNFα)–blocking agents in SAPHO syndrome is of great interest (Wagner AD, Andresen J, Jendro MC, Hülsemann JL, Zeidler H. Sustained response to tumor necrosis factor α–blocking agents in two patients with SAPHO syndrome. Arthritis Rheum 2002;46:1965–8). The authors emphasized the sustained clinical effect of TNFα blockage over a 9-month period. We have observed the same persistent efficacy of this treatment in 2 patients with SAPHO syndrome.

In the autumn of 2000, two patients with refractory SAPHO syndrome received three 5-mg/kg intravenous infusions of infliximab at weeks 0, 2, and 6. The positive results observed over a 6-month period were published in April 2002 (Olivieri I, Padula A, Ciancio G, Salvarani C, Niccoli L, Cantini F. Successful treatment of SAPHO syndrome with infliximab: report of two cases. Ann Rheum Dis 2002;61:375–6). The first patient was a 35-year-old man who had experienced severe acne and painful osteitis of the left clavicle for 17 years. After the first infusion, swelling, warmth, and tenderness of the left clavicle remitted, his severe acne dramatically improved, the C-reactive protein (CRP) level returned to normal, and the patient was able to stop using nonsteroidal antiinflammatory drugs (NSAIDs). Acne, along with swelling, warmth, and tenderness of the left clavicle reappeared 2 months after the third infusion of infliximab and disappeared again after a fourth infusion.

The second patient was a 52-year-old man with SAPHO syndrome affecting the clavicles, the sternoclavicular joints, the sternum, and the first 2 ribs. Pain, swelling, and tenderness of the manubrium sterni and both sternoclavicular joints disappeared, and the CRP level returned to normal after the first infusion, when NSAIDs were discontinued. Symptoms and signs reappeared 10 weeks after the third infusion, when we decided to proceed with a fourth infusion. Again, a complete remission was observed in 3 days.

After the fourth infusions were administered, it was decided that a fifth infusion would be given on an as-needed basis. In the following 18 months, the first patient had only a few short and mild recurrences of pain in his left clavicle, which were successfully treated with short courses of nimesulide, while the second patient had no symptoms.

The results of our study and that of Wagner et al suggest that TNFα blockage is effective in SAPHO syndrome, and that the positive results may persist for a long time, even after the end of treatment. Controlled studies with larger numbers of patients are now necessary.

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DOI 10.1002/art.11068

Reply

To the Editor:

Olivieri et al report a sustained clinical effect of infliximab over a period of 18 months in 2 patients with SAPHO syndrome (1). We have described a sustained clinical effect of continuous application of etanercept or infliximab over a 9-month period in 2 patients. Both anti-TNFα treatment modalities were well tolerated. Anti-TNFα treatment using either infliximab or etanercept reduced symptoms in the patients with SAPHO syndrome. The favorable response was

further supported by a significant reduction of the mean prednisolone dosage. Our own histologic studies revealed high levels of TNFα production in bone biopsy specimens, indicating that inflammation in SAPHO syndrome is mediated by local TNFα production. Therefore, blocking local TnFα might partly explain the beneficial effect of anti-TnFα therapies in patients with SAPHO syndrome. The report by Olivieri et al extends our findings by showing that anti-TNFα therapy of very short duration might be successful in patients with SAPHO syndrome. Thus far, this effect has not been observed in other patient populations with rheumatic diseases. Overall, the case reports by Olivieri et al support our own observations and encourage the administration of infliximab or etanercept in patients with SAPHO syndrome.

The acronym SAPHO brings together a spectrum of various manifestations and combinations of dermatologic, rheumatologic, radiologic, and histologic findings (2). We refer to Schilling et al, who elaborated for the heterogeneous clinical pictures 5 subgroups of the SAPHO syndrome in a case series of 140 patients: chronic recurrent multifocal osteomyelitis (CRMO), spondarthritis hyperostotica pustulo-psoriatica, inflammatory syndrome of the anterior chest wall, sternocostoclavicular hyperostosis, and arthroskeletal association with pustular acne (3,4). In the report by Olivieri et al, TNFα treatment had beneficial effects in one patient with osteitis of the clavicle and severe acne and in a second patient with palmoplantar pustulosis and involvement of the clavicles, the sternoclavicular joints, the sternum, and the first 2 ribs. One of our own patients who experienced sustained response to TNFα-blocking therapy presented with CRMO, with involvement of the mandible and the mandibular joint, as initially diagnosed and presented by Schilling (5,6). The leading presentation of the second patient was arthro-osteitis of the manubrium sterni and the sternoclavicular joints. Therefore, we further conclude that thus far, TNFα-blocking agents are efficient in different subgroups of patients with SAPHO syndrome.

For the future, it would be important to agree on the classification of subgroups, to standardize the diagnostic criteria, and to establish common therapeutic approaches. An international network, as proposed by Vanin and Zulian (7), in which specialists including pediatricians, rheumatologists, radiologists, and pathologists take part, giving their specialized contributions, could be the appropriate way to face this problem.

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DOI 10.1002/art.10936

Thrombotic thrombocytopenic purpura in a patient with Behçet's disease

To the Editor:

We have read about the possibility of a close relationship between certain collagen vascular diseases such as systemic lupus erythematosus (SLE) and thrombotic thrombocytopenic purpura (TTP) in childhood (1,2). We would like to report a case of TTP in a patient with Behçet's disease.

The patient, a 25-year-old woman, was admitted to the hospital because of generalized weakness, fever, jaundice, anorexia, and decreased concentration. Results of her laboratory studies showed serum creatinine 0.9 mg/dl, blood urea nitrogen 16 mg/dl, total proteins 8.1 gm/dl (albumin 3.8 gm/dl), hemoglobin 5.0 gm/dl, hematocrit 14%, leukocyte count 10,300/mm^3, platelet count 11,000/mm^3, and reticulocyte count 3%. The erythrocyte sedimentation rate was 105 mm/hour. Fragmented erythrocytes were demonstrated on blood smear. The prothrombin time and partial thromboplastin time were normal, and the serum lactate dehydrogenase (LDH) level was 870 IU/liter (normal 230–460). Total bilirubin was 7.3 mg/dl (direct bilirubin 3.1 mg/dl). Results of direct and indirect Coombs' test were negative. Cryoglobulins, antinuclear antibodies, and anti–double-stranded DNA antibodies were negative. Serum VDRL was negative, and urine analysis revealed numerous erythrocytes and rare white blood cells. Radiographs of the chest and abdomen were normal.

Based on the above findings, a diagnosis of thrombotic thrombocytopenic purpura was made. The patient received blood products and multiple plasma exchange transfusions. Within 3 weeks, she improved completely. The hemoglobin level was 15 mg/dl, the platelet count was 160,000/mm^3, and indices of hemolysis had completely normalized (LDH 134 IU/liter). Her hospital stay was complicated by lower extremity deep vein thrombosis. The thrombophila workup was negative. Her medical history revealed recurrent painful oral and genital ulcers, and upon followup, acnelike lesions had developed. A diagnosis of Behçet's disease was made. The patient was maintained on colchicine, warfarin, and prednisone. Thereafter, she did not have a relapse of TTP but had recurrent major venous thrombosis in the hepatic vein and the inferior vena cava, suggestive of vascular thrombotic complications related to Behçet's disease.

Most cases of thrombotic microangiopathy such as hemolytic uremic syndrome (HUS) and TTP are idiopathic. Some cases are related to diarrhea caused by *Escherichia coli* type O157:H7 (3), chemotherapy, cancer, and immunosup-

pressive medications such as cyclosporine. There is a possibility of an association between TTP and some collagen vascular diseases such as SLE (1,2,4). In the literature, there are no cases of thrombotic microangiopathy (HUS/TIP) related to Behçet's disease. Beaufils et al reported microangiopathic hemolytic anemia, renal failure, and thrombocytopenia in 2 patients with Behçet's disease treated with cyclosporine (5). Docci et al reported another case of a patient with Behçet's disease in whom HUS/TTP developed during treatment with cyclosporine (6). The mechanism was possibly endothelial damage by direct toxic effect of the drug (5,6). To our knowledge, this is the first case of TTP in a patient with Behçet's disease that was not induced by medications. This report may further support the presumptive association between TTP and some collagen vascular diseases.

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DOI 10.1002/art.11069

Reply

To the Editor:

We thank Jabr et al for their letter regarding the association between TTP and Behçet's disease. This letter cited our study on the close relationship between TTP and childhood-onset SLE, in which we reported that children with TTP are at high risk of having SLE concomitantly or developing this disease in the future.

As pointed out by Jabr et al, there are various forms of TTP, including familial TTP; TTP associated with viral, bacterial, or fungal infections or with use of certain medications; and TTP occurring after bone marrow transplantation (1). Known risk factors for the development of TTP are health states in which estrogen levels are raised or altered, such as pregnancy, postabortion periods, or during hormone replacement therapy (2). TTP is characterized by widespread platelet thrombi in arterioles and capillaries. Unusually large or multimeric von Willebrand factor (vWF) molecules, as well as abnormalities in one or more platelet-agglutinating factors, have been implicated in the pathogenesis of some forms of TTP as well as HUS (1,3). As such, it has been shown that at least some patients with SLE have decreased levels of vWF cleavage protein during episodes of TTP (4).

It would be of interest to know whether unusually large or multimeric vWF molecules were also present in the patient described by Jabr et al, whether she had been exposed to medications associated with TTP (including oral contraceptives), or whether she had recently undergone an abortion. Knowledge about the absence of known risk factors for TTP would support the hypothesized causal relationship between Behçet's disease and TTP. This is especially important, because the other reported patient with Behçet's disease and TTP was treated with cyclosporine, a medication with a well-established association to TTP. We also wonder whether there could truly be a causative relationship between Behçet's disease and TTP, given the relative frequency of Behçet's disease and an extreme paucity of reports of Behçet's disease in association with TTP.

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DOI 10.1002/art.10878

Some anti-proinflammatory musings: proinflammatory is inflammatory

To the Editor:

Irregardless of whether you diagnose fibromyalgia or doubt its very existence, the time has come for all thoughtful

rheumatologists to unite by voicing undivided, unanimous support for the use of the word "proinflammatory." A small coterie of unchangeable intransigents (rumored to be primarily orthopedists) cling tightly to the belief or contention that proinflammatory is an unacceptable, pleonastic redundancy, simply because the prefix "pro" contributes nothing to the word's meaning. These unhappy malcontents are merely essaying to rob and plunder a valuable, perhaps even invaluable, addition from our lexicon.

A PubMed search for articles published beginning with the year 1970 reveals "A pro-inflammatory effect of adrenaline in thermal injury" by K. L. Green and M. Ginsburg (*British Journal of Pharmacology,* 1973) as perhaps the first reference to coin either "pro-inflammatory" or "proinflammatory." As shown in Figure 1, the PubMed database demonstrates a 33-fold increase in the use of the word "inflammatory" since 1973, and nearly a 2,000-fold increase in the use of "proinflammatory" over the same period. *Arthritis & Rheumatism* is among the journals most likely to have adopted "proinflammatory," as demonstrated by some recent titles (1,2). The lingering preference for "inflammatory" presumably reflects the atavistically anachronistic and anachronistically atavistic use of phrases such as "inflammatory bowel disease" (IBD) and "chronic inflammatory demyelinating polyneuropathy" (CIDP). Changing the acronmys to PBD and CPDP, respectively, may evolve more slowly than the change from inflammatory to proinflammatory.

Rheumatologists need to take a proactive stance to steadfastly maintain the usage of proinflammatory in our journal, even if word-conscious authors risk becoming inflammatory in the eyes of grammarians.

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Author's postscript: I have shown this letter to my fifth-grade English teacher, who suggested that the meaning would be retained if the letter were revised as follows: "'Proinflammatory' is a solecism because the prefix is redundant. Unfortunately, its usage has risen exponentially. A concerted effort should be made to avoid employing this word."

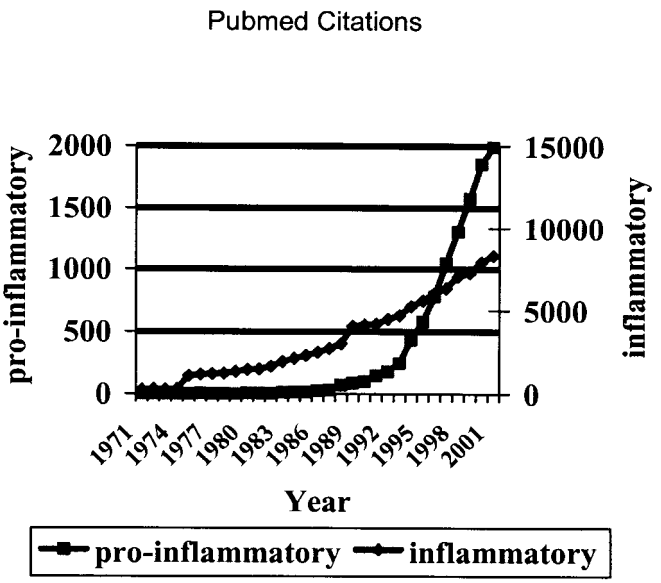

Figure 1. Usage of the term "pro-inflammatory" versus "inflammatory" in medical journals, based on citations in the PubMed database.

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