LETTERS

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Monitoring guidelines for methotrexate-treated rheumatoid arthritis patients: comment on the article by Yazici et al

To the Editor:

In a recent article, Yazici and colleagues used data from a survey of a relatively small number of rheumatologists to support the notion that a laboratory monitoring regimen for methotrexate (MTX)-treated patients with rheumatoid arthritis (RA) that is less intensive than that suggested by the American College of Rheumatology (ACR) is desirable (1). The lack of guidelines for monitoring patients receiving biologic compounds (anti–tumor necrosis factor and anti–interleukin receptor antagonist) was also noted in their report (1). The authors go on to suggest that the guidelines for monitoring MTX therapy need to be updated, and that guidelines for monitoring biologic compounds need to be drawn. Although we strongly agree with the second statement, we feel uncomfortable concluding, based on the data presented, that the ACR guidelines for monitoring MTX therapy need to be modified. Whereas these guidelines are far from being perfect, they are still the best we have; for persons unfamiliar with the original 1994 publication, the guidelines were derived from data based on sound methodology (2).

In a related matter, we want to point out that data gathered in a selected group of patients with RA (n = 313), who were followed up at less frequent intervals than those recommended by the ACR, and who only rarely presented abnormal liver function test abnormalities, were presented by Yazici et al at the 2003 annual meeting of the ACR (3). Unfortunately, these data have been quoted on the internet (e.g., eRheumatology News) as coming from the ACR, suggesting that the ACR guidelines are being “adjusted” (4). This, we think, is quite misleading to the clinician given that the ACR endorsement, and I personally had no control nor any

Is it possible that we have become too complacent in monitoring methotrexate therapy because we may not have personally witnessed a case of clinically significant liver disease? Changing the guidelines should be a meticulously data-driven process rather than based on the current practice patterns of a relatively small group of rheumatologists; at the conclusion of such a process, the guidelines may indeed be changed. If that is the case, we will be the first to welcome such change. Until then, we should use the guidelines as they are.

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Reply

To the Editor:

Thank you for the opportunity to respond to the letter by Drs. Alarcón, Kremer, and Weinblatt. With all due respect for the 8 rheumatologists on the Subcommittee on Hepatic Toxicity and MTX of the ACR who developed the current guidelines (1), the number of rheumatologists included in our study (n = 123) is 15-fold larger, representing ~5% of practicing rheumatologists in the US. These rheumatologists provided their views concerning standard, everyday care of patients with RA. Furthermore, the current guidelines appear to be based on 446 patients, rather than the quoted 700 (2), 383 of whom had been the subject of 11 previously published studies, 8 of which were continuations of 3 reports of the same patients. This methodology may have led to a misleading total.

I also agree that the current guidelines for MTX monitoring are the best we have, but they are also the only guidelines available. The assumptions concerning clinically significant liver disease rates and the risks associated with liver biopsies (3), as well as the arbitrary choice of testing intervals not supported by data (4), in the development of these guidelines have already been challenged. Other investigators have also suggested modification of the current guidelines, with less frequent laboratory monitoring (5,6). Surely the authors are not suggesting monitoring blood tests every 4 weeks, which would be the literal interpretation of these guidelines.

Drs. Alarcón, Kremer, and Weinblatt also suggest that an abstract presented at the 2003 ACR meeting about the small number of liver function test abnormalities observed among 313 RA patients was presented as an ACR-endorsed statement by a commercial Web site for rheumatologists. This was a newsreel about the abstract about MTX and liver function test abnormalities. There was no indication of an ACR endorsement, and I personally had no control nor any role in the preparation of this newsreel.

Finally, it would be of interest to learn the current prevalence of liver function test abnormalities in patients seen by Drs. Alarcón, Kremer, and Weinblatt, to compare with data reported by me and my colleagues, to help the rheumatology community judge the optimal frequency of laboratory monitoring of patients treated with MTX.

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Intravenous immunoglobulin and antiphospholipid syndrome: comment on the article by Erkan et al

To the Editor:

We read with interest the article by Erkan et al addressing the recent consensus on the diagnosis and treatment of the catastrophic antiphospholipid syndrome (CAPS) and focusing on the latest advances (1). In their report, Erkan et al consider intravenous immunoglobulin (IVIG) as a therapy to be used in addition to anticoagulants and steroids in cases of life-threatening conditions, specifying that IVIG is well tolerated but is contraindicated in patients with IgA deficiency. However, the authors do not mention that arterial or venous thrombotic events following IVIG infusion have been reported (2–4).

The place of IVIG in the therapeutic arsenal for APS must be defined, even though IVIG has been shown to improve pregnancy outcome in association with use of anticoagulants and aspirin (5). However, CAPS constitutes a very special condition related to APS that can be difficult to distinguish from thrombotic thrombocytopenic purpura (TTP), as Erkan pointed out. We previously reported the case of a 42-year-old woman with idiopathic TTP whose neurologic symptoms seriously worsened immediately after IVIG infusion, making the use of IVIG questionable in the acute phase of the disease (6). In such cases, we believe that use of IVIG might be deleterious. Moreover, in the series of 80 patients affected by CAPS reported by Asherson et al in 2001 (7), there was no difference regarding recovery between patients who had received IVIG and patients who had not. However, only 15 of 80 patients (19%) received IVIG; this small number prevents drawing any conclusion.

The mechanism of IVIG-related thrombosis remains unclear, but a rise in blood viscosity dependent on the dose infused is suspected; this rise could last for up to 1 month (8). In addition, IVIG could enhance platelet aggregation, activate the coagulation cascade, as well as mediate vasospasm (9,10). In conclusion, the safety of IVIG in the treatment of CAPS cannot be warranted, and IVIG should be used very cautiously given the risk of accelerating the so-called clotting storm. In the absence of more evidence, we think that plasma exchange should be preferred to IVIG in the acute phase of CAPS.


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Intravenous immunoglobulin and antiphospholipid syndrome: comment on the article by Erkan et al

To the Editor:

We thank Jean et al for their comments on our recent article. CAPS has now been researched for 12 years, and we do believe, based on the information available on 130 documented and analyzed patients (1,2) as well as a further 100 cases now in the CAPS registry (3), that IVIG should definitely be included among the major therapeutic options for patients...
with this unusual and often fatal syndrome. Due to the small number of IVIG-treated patients thus far, statistical evidence may not be available at the present time; however, we believe that with the increasing number of reported cases and the more frequent use of IVIG, this evidence will be forthcoming in future analyses. Our reasons for the use of IVIG in CAPS patients are as follows.

1. IVIG has successfully been used in both experimental APS animal models (4) and APS patients with pregnancy morbidities (5). The mode of action of IVIG is antidiotypic, directed to antiphospholipid antibodies, leading to immunomodulation of their pathogenetic role (5).

2. Based on our analysis of the CAPS registry, in the presence of an inadequate response to anticoagulation and corticosteroids, either IVIG or plasma exchange clearly improves the outcomes (3,6). However, currently it is unknown whether the addition of plasma exchange is superior to the addition of IVIG, and the outcomes of patients receiving anticoagulation, corticosteroids, and IVIG are not different from those of patients receiving anticoagulation, corticosteroids, and plasma exchange (3).

3. There have been a few reports of thrombosis with IVIG when it is used at doses higher than those recommended (>0.4 gm/day per kilogram of body weight), administered at a rate of infusion higher than that recommended, or in the presence of other major thrombotic risk factors (7,8). The 42-year-old patient with TTP mentioned by Jean et al and described by Duran et al in 1994 is an excellent example of these concerns (9). That patient had been receiving oral contraceptives at the time of TTP diagnosis, received IVIG at a dose of 0.5 gm/kg of body weight, and neurologic deterioration occurred 4 hours after the infusion (the infusion rate is not reported).

4. Based on our experience in IVIG-treated CAPS (1–3) and non-CAPS patients (10), we did not encounter a single event of thromboembolism attributable to IVIG.

5. Also as noted by Jean et al, TTP and heparin-induced thrombocytopenia share similarities with CAPS, and IVIG has been successfully used for these conditions (11–12).

6. Infections may play a triggering role in many CAPS patients, and IVIG has a broad spectrum of antibacterial and antiviral activity (13). Thus, treating CAPS patients with IVIG may offer additional therapeutic advantages.

7. Plasma exchange can be associated with its own complications. As noted by Duran et al, the sudden rebound of the antiphospholipid antibodies following plasma exchange can contribute to thrombotic microangiopathy, and plasma exchange should be used cautiously in the absence of immunosuppressive therapy (14).

In summary, due to the low frequency of side effects encountered with IVIG (15) in addition to the multiplicity of therapeutic actions seen with this compound, and the fact that all CAPS patients, in any event, are receiving full doses of anticoagulation therapy simultaneously, IVIG should absolutely be included in the therapeutic armamentarium offered to these patients, who have a potentially life-threatening condition.


HLA–DQA1 as a risk factor for microchimerism: comment on the article by Artlett et al

To the Editor:

The recent article by Artlett et al (1) addresses the topic of whether specific HLA alleles are associated with persistent microchimerism, a potential risk factor for autoimmune diseases, as described previously (2). Because the results of the study by Artlett et al are described in comparison with our previous report, I would like to clarify a few descriptions that are not correct. Artlett and colleagues state that, in contrast to our study, they did not find the HLA–DQA1*0501 allele or any other DQA1 allele to be a risk factor for fetal microchimerism in either T lymphocytes or whole peripheral blood from the SSC patient cohort or the controls. First, we never tested whole peripheral blood in our study. Second, although DQA1*0501 was more frequent among women with fetal microchimerism within T lymphocytes, as stated in our article, this finding was not significant when corrected by the number of alleles tested. I am not surprised that Artlett et al did not observe an association with the host's genotype.

In our study, we observed that fetal microchimerism was more common among women with fetal microchimerism within T lymphocytes, as stated in our article, this finding was not significant when corrected by the number of alleles tested. I am not surprised that Artlett et al did not observe an association with the host's genotype.

To ascertain important variables such as the total amount of DNA tested and the purity of sorted subsets. Furthermore, results were combined from quantitative and nonquantitative assays (e.g., a weaker third band was classified as the microchimeric allele), and the criteria used to categorize individuals as positive or negative were not defined. Moreover, quantitative and nonquantitative techniques show different sensitivities, with, respectively, a sensitivity of 1 male cell in 100,000 (IL-10) production by peripheral blood mononuclear cells (PBMC) cultured with α1(I) and α2(I). This dosage of CI also reported—representing levels as high as 1% of all circulating cells

Methods to detect and accurately quantify microchimerism have advanced considerably since our study in 2000. Further studies will be necessary, in which standardized and carefully conducted techniques are used to study larger numbers of individuals. A final issue we previously raised is whether patients with autoimmune diseases who lack disease-specific HLA molecules could be investigated for persistent microchimerism as an alternative source of HLA disease–associated molecules or peptides, whereas patients who have the disease-specific HLA molecules might not have persistent microchimerism. This is one potential explanation for the observation by Artlett et al that DQA1*0501 was frequently observed in patients who were negative for microchimerism, even though juvenile idiopathic inflammatory myopathy is frequently associated with DQA1*0501.

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Dosage effects of orally administered bovine type I collagen on immune function in patients with systemic sclerosis

To the Editor:

Type I collagen (CI), the most abundant protein in humans, may play a pivotal role in the pathogenesis of systemic sclerosis (SSc) (1–6). Oral tolerance studies in rodents have shown that the dose-response curve for orally administered antigen is bimodal, with tolerance being induced optimally using low and high doses of antigen (7). It has been postulated that high-dose oral antigen induces predominantly clonal deletion of antigen-specific T cells, while low-dose oral antigen induces regulatory T cells (8,9). Work from our institution has demonstrated that oral administration of CI at 500 µg/day in patients with SSc induces tolerance, as characterized by significant reductions in interferon-γ (IFNγ) and interleukin-10 (IL-10) production by peripheral blood mononuclear cells (PBMC) cultured with α1(I) and α2(I). This dosage of CI also

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effected improvement in several disease parameters, including skin scores (modified Rodnan skin scores [MRSS]) (10), patient assessment of disease activity (modified Health Assessment Questionnaire [M-HAQ]) (11), and results of pulmonary function tests (PFTs), including diffusing capacity for carbon monoxide (DLco) and forced vital capacity (FVC) (12).

Studies in humans with rheumatoid arthritis (9), as well as in animals (13,14), suggest that the oral dosage of an autoantigen such as collagen is pivotal in determining whether tolerance occurs and disease activity is suppressed. In our previous study of oral CI administration to patients with SSc, we used high doses of collagen (500 µg/day) and did not explore the effects of lower-dose regimens (12). The purpose of the present study was to determine whether lower doses of oral CI (10 µg/day and 100 µg/day) would induce immune tolerance to CI in patients with SSc, and/or whether a change in clinical parameters could be effected after 5 months of administration of CI at either or both of these dosages.

The study population consisted of 4 men and 18 women with SSc (17 white, 5 African American). Patients were recruited from the University of Tennessee (UT) and community rheumatology practices in Memphis and surrounding areas. The mean ± SD duration of disease in the study population was 6.7 ± 7.5 years (range 1 month to 30 years). Eight patients had limited SSc and 14 had diffuse SSc. Written consent for participation in the study was obtained from patients in accordance with the Helsinki II declaration, and the protocol was approved by the UT Institutional Review Board.

The study was conducted under US Food and Drug Administration Investigational New Drug application 6575. The inclusion criterion was a clinical diagnosis of limited or diffuse SSc. The exclusion criterion was a clinical diagnosis of limited or diffuse SSc. The rationale for the exclusion of NSAIDs was not allowed. The rationale for the exclusion of NSAIDs was based on work from our institution suggesting that NSAIDs may impede the development of oral tolerance (16).

For the first 5 months, all patients received placebo (0.1M acetic acid). Patients were then randomized to receive CI at 10 µg/day or 100 µg/day for 5 months. Those who had received the 10 µg/day CI dosage for 5 months were then crossed over to receive the 100 µg/day dosage for 5 months, and vice versa. Collagen was solubilized in 0.1M acetic acid and aliquoted into individual-dose vials which the patients kept refrigerated. Each morning, the patient added 1 vial of the CI preparation to 4–6 ounces of orange juice, and this was consumed before breakfast. Compliance was monitored by counting the milliliters of study drug left in vials returned at each visit. Patients were considered to have complied with the protocol if they have consumed at least 70% of the study medication. The mean consumption was 88.8% (range 71.2–96.9%).

All assessments were performed at 0, 5, 10, and 15 months. The MRSS (assessed by the same trained physician throughout) and the M-HAQ score were recorded. PFTs, including FVC and DLco studies, were performed by the same technician (under the direction of a pulmonologist), using the same equipment each time. IFNγ and IL-10 levels were measured, by commercial enzyme-linked immunosorbent as-

Data were analyzed in a covariance structural model to fit a crossover design (PROC MIXED, version 9.1; SAS Institute, Cary, NC). Analyses were performed to determine whether there were significant differences in the mean responses to collagen at 10 µg/day versus 100 µg/day, collagen at 10 µg/day versus placebo, and collagen at 100 µg/day versus placebo. Results were adjusted for baseline measurements (including MRSS, M-HAQ score, PFT results, and cytokine levels), age, race, sex, disease duration, and type of SSc (limited versus diffuse).

Eighteen patients received 5 months of placebo treatment, 14 received at least 1 dose of oral CI, and 11 completed the entire study. The 11 study withdrawals were due to issues regarding compliance (n = 6), traumatic Colles fracture (n = 1), intercurrent medical illnesses not related to SSc (n = 2), pregnancy (n = 1 [during placebo treatment]), and allergic reaction to collagen characterized by a skin rash (n = 1). The final sample size was similar to that in our previous study, in which only 17 patients completed the protocol, and of these, only 11 actually had PFTs performed (12). Despite these small numbers, statistically significant results had been demonstrated for immune and clinical parameters, including PFT results, after 1 year of treatment with oral bovine CI at 500 µg/day (12).

There were no significant differences in response to CI at either 10 µg/day or 100 µg/day compared with placebo, with respect to clinical parameters including MRSS, M-HAQ score, and PFT results (FVC and DLco). Interestingly, there was a significant increase in IFNγ production in response to α2(I) by PBMCs from patients receiving CI at 100 µg/day compared with both the placebo group (P = 0.02) and the 10 µg/day CI group (P = 0.01). There were no significant differences in the IFNγ response to α1(I) or in the IL-10 response to α1(I) or α2(I) among the treatment groups. In addition, levels of sIL-2R did not differ among the groups (P > 0.05).

The major finding of our study was that there was no significant response in any of the clinical parameters evaluated, including MRSS, M-HAQ, or PFTs, to oral bovine CI administered at either 10 µg/day or 100 µg/day for 5 months. Furthermore, there was no suppression of the T cell response to CI (i.e., reduction in IFNγ and/or IL-10 production) and no change in systemic immune activity. However, with the 100 µg/day dosage of CI, we did not note increased in vitro production of IFNγ; this response was seen with α2(I) stimulation, but not α1(I) stimulation. Increased IFNγ production by peripheral lymphoid cells cultured with tolerizing antigen has been associated with induction of tolerance to some orally administered antigens in humans and mice (17,18). Whether this enhanced IFNγ production in response to α2(I) represents tolerance induction or whether increased production of endogenous IFNγ is beneficial in SSC requires further investigation. Induc-
tion of IFNγ may be important because of the antifibrotic properties of this cytokine (19).

It should be noted that our results are limited by the small number of patients who completed the study, the wide range of disease duration, and the probable need to administer oral CI for longer than 5 months to observe a change in skin scores or pulmonary function. However, our findings suggest that low-dose CI may have some effect on cytokine profiles in SSc, although no response in any clinical parameters was noted.

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Recommendations regarding individuals in whom bone densitometry should be performed: comment on the article by van Staa et al

To the Editor:

We read with great interest the article by van Staa and coworkers on the bone mineral density (BMD) threshold for prediction of vertebral fractures in patients receiving oral glucocorticoid therapy (1). Compared with non–glucocorticoid users, glucocorticoid users appear to develop fractures at a higher BMD. The American College of Rheumatology recommends therapeutic intervention if the T score for BMD is below –1 in a patient who has had long-term treatment with glucocorticoids (2). The UK National Osteoporosis Society advocates intervention at a T score threshold of –1.5 (3). With the increasing use of bone density testing for diagnosing osteoporosis and establishing fracture risk, inconsistencies have arisen in the way in which bone densitometry is performed and the results interpreted. As an example, T score diagnostic thresholds for postmenopausal Caucasian women not exposed to glucocorticoids may not apply to patients who are receiving glucocorticoid therapy. A similar analogy could be made in applying World Health Organization T score criteria to men and premenopausal women.

To reduce these inconsistencies and improve interpretation and reporting of BMD, the International Society for Clinical Densitometry (ISCD) periodically convenes Position Development Conferences (PDCs). The most recent PDC was held in Cincinnati, Ohio, in July 2003. The ISCD is a not-for-profit multidisciplinary professional society with a mission to

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enhance knowledge and quality of bone densitometry among health care professionals. In addition, it provides continuing education courses for clinicians and technicians, and it supports clinical and scientific advances in the field.

The decision on whether to initiate therapeutic intervention must be made on the basis of knowledge of the individual patient and his/her associated risk factors, not on the basis of a numerical score. However, one of the goals of a professional society is to standardize the understanding of the field as much as possible based on evidence, as exemplified in the report by van Staar et al.

The ISCD recommends BMD testing in the following individuals: 1) women age 65 and older; 2) postmenopausal women under age 65 with risk factors; 3) men age 70 and older; 4) adults with a fragility fracture; 5) adults with a disease or condition associated with low bone mass or bone loss; 6) adults taking medications associated with low bone mass or bone loss; 7) anyone being considered for pharmacologic therapy; 8) anyone being treated, to monitor treatment effect; and 9) anyone not receiving therapy in whom evidence of bone loss would lead to treatment.

A complete review of all ISCD official positions is published in the Journal of Clinical Densitometry (4). A summary of the ISCD official positions is available online at the ISCD Web site (www.iscd.org), where there is also a viewable and downloadable slide presentation of the positions.

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Reply
To the Editor:

If we understand Dr. Ehrlich correctly, he takes issue with our article identifying subgroups of fibromyalgia (FM) patients based on the underlying mechanisms, because he 1) feels as though the FM label may cause more problems than it helps, and 2) is bothered by litigation and other contentious issues surrounding this diagnosis.

Before responding to these issues, it strikes us as odd that we need to do so. All rheumatic diseases are associated with some of the same underlying issues as those associated with FM. Most of our current “disease”

No justification for publication of study on subgrouping of fibromyalgia patients: comment on the article by Giesecke et al

To the Editor:

The diagnosis of fibromyalgia continues to be a contentious and disputed issue in rheumatology. As Sherine Gabriel puts it, citing Cohen and Quinter, “Diagnostic criteria for fibromyalgia convey no pathophysiologic insight and . . . have been validated via a circular argument in which the evidence on which the construct is based is taken as proof of its veracity” (1). Thoughtful rheumatologists have abandoned this untenable concept.

Nonetheless, a study recently presented in Arthritis & Rheumatism (2) even creates subgroups (!) based on pressure-pain thresholds and psychological factors. The fact that this makes little sense from the standpoint of evidence-based medicine or science did not prevent it from being published. This article ranks with the many presentations at the American College of Rheumatology meetings in Orlando this year devoted to this portion of the chronic pain spectrum that serves to delight litigators and their allies and that has made the diagnosis an industry, with a plethora of “journals” published by Haworth Press, but no justification for validation by publication in Arthritis & Rheumatism.

Furthermore, in an article appearing in the same issue of Arthritis & Rheumatism in which the report by Giesecke et al appears, Conte and colleagues rightly place the afflictions of the children described in the pain syndromes but then, without justification, classify their problems as fibromyalgia (3). To quote from the ACP Observer, “A label can be counterproductive for people who are particularly susceptible to suggestion and playing the sick role” (4).

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criteria are defined largely upon historic notions of what constituted an illness, and those constructs have fundamental flaws if they are critically examined. However, although we endeavor to better understand any illness, these labels and constructs help us understand the underlying cause of a patient’s symptoms, as well as how to treat the individual.

In osteoarthritis, for example, if the underlying “disease” is joint space narrowing and osteophyte formation, then why do 30–50% of patients in the population with the most severe forms of this disease (e.g., Kellgren/Lawrence grade 3 or 4 changes) have no pain or symptoms (1,2)? In systemic lupus erythematosus (SLE), if the “disease” is characterized by immune complex formation and subsequent tissue damage, then why don’t indices measuring the extent of disease activity or symptoms correlate well with the symptoms SLE patients are experiencing (3–5)? When peer-reviewed scientific articles on the underlying mechanisms of these disorders are published in Arthritis & Rheumatism, the authors generally are not asked to address questions regarding the legitimacy of the underlying diagnosis.

As with these other rheumatic disorders, there is much we must learn regarding FM. However, just as with these other disorders, the overwhelming majority of patients who are given the FM label are helped: this reduces unnecessary further diagnostic testing and gives both patients and physicians a construct with which to help understand the underlying mechanisms and, most importantly, the most effective treatments. To illustrate this point, imagine if the American College of Rheumatology criteria for FM had not been established. We would have nothing to “call” individuals with the second most common rheumatic disease, and no way of standardizing studies elucidating the underlying mechanisms or most effective treatments. Would that really represent a better state of affairs?

The most unfortunate aspect of this letter, and editorials and opinion pieces in the same vein, is that they perpetuate many of the myths and stereotypes regarding FM that research has shown to be untrue (6,7). The label of FM does not lead to an increase in the prevalence of FM, nor does it escalate illness behavior (8). In many patients with the FM syndrome, psychosocial factors play a role in symptom expression, but worsen symptoms only in some individuals. In fact, in our article, psychosocial factors appeared to make the underlying FM symptoms better rather than worse, in ~20% of patients with FM. Finally, it is true that a small minority of patients with FM, just as with almost any other medical disorder, become overwhelmed by the demands of their illness and predicament and seek solace by applying for disability or pursuing legal action. The undersigned authors are just as troubled as Dr. Ehrlich by these “outliers” who become permanently disabled or receive large damages, but we differ in how we choose to respond to the problem.

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Tumor necrosis factor α blockade as therapy for sarcoidosis: comment on the article by Ulbricht et al

To the Editor:

We read with great interest the report by Ulbricht and coworkers about successful treatment with infliximab of a patient with therapy-resistant systemic sarcoidosis (1). Even though a previous report by Yee and Pochapin (2) is referenced, the authors go on to state that, “To our knowledge, this is the first case of successful treatment of typical therapy-resistant multiorgan sarcoidosis.” We would like to point out to the readers of Arthritis & Rheumatism that the concept of anti-tumor necrosis factor α (anti-TNFα) therapy for sarcoidosis is not new, that depending on the agent used, anti–TNFα therapy has had mixed results, and that this treatment concept is currently undergoing active further investigation.

As pointed out by Ulbricht et al (1), there is a good scientific rationale for TNFα inhibition in sarcoidosis (3). Based on this rationale, 4 agents have been tried in sarcoidosis: pentoxifylline, thalidomide, etanercept, and infliximab. Pentoxifylline was the first anti-TNFα agent used in sarcoidosis...
This drug inhibits the secretion of TNFα by activated monocytes and alveolar macrophages in vitro. To date, the reported clinical success of pentoxifylline has not been corroborated, but a formal prospective trial is currently ongoing at the National Institute of Health (http://clinicaltrials.info.nih.gov/detail/A_99-H-0057.html). Thalidomide, which selectively suppresses TNFα production by enhancing degradation of TNFα messenger RNA, has also been reported to be of benefit in patients with refractory sarcoidosis (6,7). Recombinant protein TNFα inhibitors designed to neutralize circulating TNFα have recently become available, and etanercept and infliximab have been used in sarcoidosis. A recently performed open-label prospective trial of etanercept showed disappointing results in the treatment of stage II or III progressive pulmonary sarcoidosis, because the number of early treatment failures had triggered the early-stop rule of the trial (8).

In contrast, the reported experience with infliximab in sarcoidosis seems to be more encouraging. Nine cases, including the one described by Ulbricht et al, of successful infliximab use in sarcoidosis have been reported to date (1,2,9–13). The reported dramatic symptomatic and objective responses are indeed striking and include the most difficult situations such as neuro- or cardiac sarcoidosis. In addition, there have been severa presentations at meetings, with published abstracts, that indicate similarly promising results. Although these reports on infliximab in sarcoidosis are encouraging, the number of patients with “therapy-resistant” sarcoidosis, who have failed to respond to infliximab, remains unknown. Therefore, the indiscriminate use of this agent in steroid-dependent sarcoidosis should be discouraged, and the results of an ongoing multicenter prospective randomized trial comparing infliximab with placebo in patients with chronic steroid-dependent sarcoidosis (http://www.clinicaltrials.gov/ct/show/NCT00073437) are eagerly awaited. We hope that results as promising as those reported by Ulbricht et al will be confirmed by the formal trial.

The failure of etanercept in pulmonary sarcoidosis should not lead to skepticism about the use of infliximab in sarcoidosis. Even though both agents effectively neutralize TNFα, different clinical effects of the 2 agents have been well documented in Crohn’s disease (14–16). Documented properties of infliximab that are not shared with etanercept include its ability to bind to peripheral blood lymphocytes and lamina propria T cells, and to induce apoptosis of activated lymphocytes (17). These properties and possible differences in tissue bioavailability may explain the observed differences in efficacy between different anti-TNFα agents in granulomatous diseases such as sarcoidosis.

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Reply

To the Editor:

We thank Dr. Specks and his colleagues for their interest in our article. Dr. Specks et al give a sophisticated summary of the literature concerning treatment concepts in sarcoidosis. Six articles are cited describing infliximab therapy in sarcoidosis (1–6), but none of them fulfills all of the criteria described in our case presentation.

We described a female patient with severe sarcoidosis involving the lung and liver, who also had arthritis. Various treatment regimens with azathioprine, methotrexate, cyclophosphamide, and pentoxifylline failed to control the disease. Infliximab therapy induced radiologic remission of the pulmonary and liver involvement and brisk clinical benefit for arthritis. Yee and Pochapin (1) presented an “unusual case of...
sarcoidosis, manifested by severe protein-losing enteropathy and proximal myopathy." In another 3 case reports cited by Specks et al (2,4,5), patients with cutaneous, pulmonary, and/or brain manifestations, but not widespread multiorgan involvement as in our patient, in whom sarcoidosis was partly refractory, are described. In an additional 2 case reports of treatment of sarcoidosis involving several organs, improvement was observed in only 1 organ (3,6).

We agree with Dr. Specks on the necessity for standardized clinical trials to study the efficacy of TNFα blockade in sarcoidosis. The indication for infliximab therapy has to be clearly defined. Should TNFα blockade be reserved for therapy-resistant sarcoidosis? Is there a need for adjuvant immunosuppression with conventional drugs such as azathioprine or methotrexate, or additional TNFα blockade with pentoxifylline or thalidomide? However, for patients such as the one described by our group, who are vitally threatened by progressive liver failure, TNFα blockade with infliximab is a promising new treatment modality.

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Variant chronic infantile neurologic, cutaneous, articular syndrome due to a mutation within the leucine-rich repeat domain of CIAS1

To the Editor:

The chronic infantile neurologic, cutaneous, articular syndrome (CINCA syndrome), also called neonatal-onset multisystem inflammatory disease (MIM no. #607115), is a devastating autoinflammatory disease (1). It is characterized by a neonatal onset with recurrent fever attacks and skin rash. Neurologic manifestations can range from headache due to chronic aseptic meningitis, seizures, and spasticity to psychomotor deterioration. Progressive sensorineural hearing loss and visual impairment, due to optic papillitis and anterior uveitis (2), contribute to the long-term disability. Arthropathy affecting the large joints may lead to contractures. The chronic persistent inflammatory response may end in secondary amyloidosis. Most cases of CINCA syndrome are due to mutations in the CIAS1 gene (3). Mutations in this gene cause a spectrum of allelic autoinflammatory disorders (4–8). CINCA syndrome represents the severe end of the disease spectrum. The CIAS1 gene encodes cryopyrin. This protein consists of an amino terminal pyrin domain, a central nucleotide-binding oligomerization domain (NOD), and a carboxy-terminal leucine-rich repeat (LRR) domain. To date, all known disease-causing mutations in CIAS1 have been found within or close to the region encoding the NOD domain. Herein we describe a patient with a predominantly neurologic phenotype and a novel de novo mutation affecting the LRR domain of CIAS1.

The patient was referred to us at the age of 16. He had been well until the age of 2 years, when he developed recurrent pains in the ankles, knees, and back, without visible joint abnormalities. At age 5 years, he developed malaise, weakness, and intermittent headaches with morning vomiting. Symptom-free intervals never lasted longer than 2 weeks. Initially, he had had a transient erythematous eruption over the cheeks, ears, and elbows, but this did not recur. He never had any conjunctivitis, oral ulcers, joint swelling, diarrhea, rectal blood loss, or lymphadenopathy. Fever was notably absent. However, a progressive sensorineural hearing loss developed, necessitating the use of hearing aids. Gradually, from the age of 4 years onward, growth deteriorated, with height dropping from the fiftieth percentile to below the third percentile for age, whereas head circumference rose from the seventy-fifth percentile to above the ninety-seventh percentile at the age of 16.

Treatment with nonsteroidal antiinflammatory drugs, 5-aminosalicylic acid, and colchicine had been ineffective. Oral prednisone (0.5–1 mg/kg per day) provided only partial relief.

Physical examination of the patient at the age of 16 years revealed a prominent forehead and delayed pubertal development (Tanner stage P2G2, testicular volume 6 ml). Anterior spinal flexion was reduced. The peripheral joints were not swollen, painful, or inflamed, and although he moved rather stiffly, passive motion of the arms and legs was not impaired. Digital clubbing was prominent. Meningism was absent.

Retinal fluorescent angiography showed papilledema, with dye leaking from central vessels. Audiography revealed a bilateral sensorineural hearing loss of 40–70 dB. Findings on blood tests had been persistently abnormal, with mild microcytic anemia, thrombocytosis, leukocytosis, granulocytosis, and eosinophilia. Throughout the entire disease course, erythrocyte sedimentation rate values ranged from 45 to 92 mm/hour, and the C-reactive protein level varied between 60 and 140 mg/liter. Immunoglobulins were polyclonally elevated, and the complement CH50 level was raised. The results of extensive serologic studies for autoimmune abnormalities had been consistently negative. The urine contained no cells or protein. Consecutive computed tomography scans and magnetic resonance imaging of the brain had shown slightly enlarged cerebrospinal fluid (CSF) spaces, but otherwise no abnormalities. At the age of 16 years, the patient’s CSF pressure was elevated (26 cm H2O), as were the CSF protein level (1.31 gm/liter) and the leukocyte count (175/μl; mainly neutrophils, eosinophils, and monocytes).
All 9 exons of the CIAS1 gene were amplified using the polymerase chain reaction as described by Hoffman et al. (8). The amplicons were directly sequenced. We identified an A2685G transition in exon 6 encoding a Tyr859Cys missense mutation (TAT-TGT). Tyr859Cys is located in the third of 7 LRRs present in cryopyrin. Neither of the patient’s parents carried this mutation. Non-paternity was excluded, suggesting that this is a de novo mutation, although the possibility of mosaicism in one of the parents cannot be excluded. Analysis of 50 normal chromosomes did not reveal this alteration. We therefore conclude that Tyr859Cys is a disease-causing mutation. Disease-causing mutations affecting the LRR domain of cryopyrin have not been reported before (Infevers database: http://fmf.igh.cnrs.fr/infevers).

The clinical phenotype in the patient described herein seems to differ from that of CINCA or Muckle-Wells syndrome in that fever, arthritis, and rash have been largely absent during his disease course. Whether this variant phenotype is truly due to altered function of the LRR can only be ascertained when additional cases in which the mutation affects the LRR rather than the NOD are identified. However, mutations in a closely related gene, NOD2, do give rise to different phenotypes depending on the affected domain. Mutations affecting the NOD of NOD2 cause Blau syndrome (MIM no. #186580), characterized by early-onset granulomatous inflammation of the joints, eyes, skin, and cranial nerves (9), whereas mutations affecting the LRR domain lead to familial Crohn’s disease (10), a distinct phenotype of granulomatous inflammation.

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