INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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Should Anti-Tumor Necrosis Factor–α Be the First Therapy for Rheumatoid Vasculitis?

To the Editor:

The risk of vasculitis following tumor necrosis factor-α (TNF-α) blockade remains controversial[1-3]. In 2002, we reported a successful response to the chimeric anti-TNF-α monoclonal antibody infliximab in a patient with biopsy-proved rheumatoid vasculitis presenting with mononeuritis multiplex who was refractory to cyclophosphamide (CYC)[4].

High-dose steroid and intravenous CYC are the cornerstone therapy in rheumatoid vasculitis[5]. However, CYC is potentially associated with the development of ominous side effects[6], and in some cases this therapy does not result in improvement of the vasculitis[4,5].

Anti-TNF-α therapy is indicated in rheumatoid arthritis (RA) patients with severe and refractory disease[7]. In our unit we have recently established a protocol for the management of RA patients with rheumatoid vasculitis using anti-TNF therapy instead of intravenous CYC. Following this procedure, we had the opportunity of treating a 73-year-old man who developed foot drop. He had a seropositive and erosive RA of 25 years' duration treated with several disease modifying antirheumatic drugs, including methotrexate and more recently leflunomide. One month before admission he began to notice weakness of his right foot. On examination, paresis on dorsiflexion of the right foot was found. Erythrocyte sedimentation rate was 85 mm/h. Chest radiograph and routine biochemistry profile including renal and hepatic function tests, antinuclear antibodies, antinative DNA, C3 and C4, and anticardiolipin antibodies were negative or normal. Electromyography result was consistent with mononeuritis multiplex, and biopsy of the right sural nerve showed focal and segmental necrotizing arteritis of small and medium-size arteries with fibrinoid necrosis and neutrophil infiltration in the artery wall. He was diagnosed as having rheumatoid vasculitis. Therapy with leflunomide was discontinued. Treatment with methotrexate (15 mg/week) was restarted and anti-TNF-α monoclonal antibody (infliximab) therapy was started. Infusion of infliximab at a dose of 3 mg/kg body weight was administered according to the standard protocol of therapy (at Weeks 0, 2, 6, and 14 and then every 8 weeks). Again, as described[3,4], 6 weeks after the initiation of infliximab therapy the motor dysfunction had regressed markedly.

Taken together, all these reports support the potential use of anti-TNF-α therapy in the treatment of neuropathy associated with rheumatoid vasculitis. However, in keeping with Richette, *et al*[1], a prospective controlled study should be performed to confirm the promising results observed so far.

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Dr. Richette and Dr. Bardin reply

To the Editor:

We read with interest the letter from Dr. Garcia-Porrua and colleagues describing another case of successful treatment of rheumatoid vasculitis-associated mononeuritis with infliximab. The authors use anti-TNF-α blockers as a first-line therapy instead of intravenous cyclophosphamide to treat patients with rheumatoid vasculitis. Some clinicians have previously reported the efficacy of TNF-α-blocking therapy during rheumatoid vasculitis[1,2].

By contrast, we and others have observed cutaneous[3], neurological[4,5], or antineutrophil cytoplasmic autoantibody-related[6] vasculitis induced by anti-TNF-α agents. In this context, the use of TNF-α blockers during rheumatoid vasculitis may be hazardous. Although the scientific interest of a single case observation is of limited value, it may alert us to potential side effects. We need a definitive controlled trial to ascertain the efficacy of anti-TNF-α agents to treat rheumatoid vasculitis.

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Definition of Clinical Differences

To the Editor:

The article by Wolfe, *et al*[1] compares the mean scores on the Health Assessment Questionnaire (HAQ) and the Physical Component Scores (PCS) of the Short Form-36 (SF-36) in different patient groups, using 6 different anchors to define these groups. The mean difference found between these groups is called Really Important Differences (RID). They chose as anchors for determining RID several clinical and societal outcomes, such as independence in participation activities versus not, or total joint replacement versus no total joint replacement. In this way they attach meaningful anchors to scores on the HAQ and the PCS of the SF-36. This is a very useful contribution to the interpretation of scores on the HAQ-DI and PCS by clinicians and patients. We would like to comment on 2 points.

Extrapolation of group differences to individual changes. We criticize the extrapolation of their cross-sectional findings about differences between groups to improvements in individual patients in randomized controlled trials (RCT) or clinical practice. First, the authors make no distinction between really important difference (RID) and really important change (RIC). They use these concepts interchangeably, which leads to confusion. An illustrative example appears in their Table 2: patients without a total joint replacement have more favorable scores on the HAQ and PCS than patients with a total joint replacement. This would suggest that surgery to replace a joint leads to deterioration of health. This shows that "really important change" cannot be derived directly from "really important difference." RID considers the differences between (groups of) individuals, while important improvements refer to changes within (groups of) individuals. To assess RID, different groups of patients are compared cross-sectionally, while RIC concerns intra-individual changes, which are assessed longitudinally by following the same individuals over time.

Second, Wolfe, *et al* present the mean scores and standard deviations (SD) on the HAQ and PCS of the SF-36 for different groups of patients. All SD are rather large, which means that there are substantial differences between patients. Consider for instance a patient scoring 0.80 on the HAQ, exactly the mean score of patients who are not work-disabled (Table 2 of Wolfe, *et al*). Is it safe to assume that this patient is really able to work? Not at all, as the 95% confidence interval of the work-disabled patients runs from 0.32 to 2.78 (i.e., 1.55 ± 1.96*0.63), provided the scores are normally distributed. It is obvious that a given work-disabled patient does not necessarily have to experience a "really important" improvement of 0.74 points (100% of RID) on the HAQ in order to regain the ability to work. In fact, in individual cases the necessary improvement, in terms of HAQ score change, may be smaller or much larger. Therefore, one should be cautious in extrapolating these group findings to individual patients.

Objections against the minimal clinically important difference (MCID). The authors point out a number of objections to MCID, which are in their opinion not encountered by defining RID. As we do not agree with any of these, we will react to them one by one.

Wolfe, *et al* state that "MCID represents a minimally clinically important (or detectable) change, which may be neither clinically meaningful nor useful." This objection has to do with the fact that they consider the MCID to be synonymous with the minimally detectable difference. They state that "A widely adopted approach for defining meaningful change is to identify the minimally clinically important difference (MCID), or the minimal detectable improvement perceptible to patients." However, the widely adopted definition of Jaeschke, *et al*[2] for MCID being "the smallest difference in score in the domain of interest which the patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management," clearly points to the importance of the change for patients and/or importance for clinical management. Note that in this definition MCID concerns a clinically meaningful change, and it does not contain any reference to what is minimally detectable[2].

Furthermore, Wolfe, *et al* see the dependence of MCID on baseline values as a disadvantage. However, this dependence is real and functional. For instance, if "independence in participation" is considered to be an important goal, patients who are close to this value need a smaller change than those patients whose baseline values are far from that intended score. This also holds for really important changes or differences.

As second objection, Wolfe, *et al* mention that "as MCID identifies a minimal detectable improvement rather than deterioration, it is not possible to interpret the magnitude of change patients perceive to be important." MCID might focus on improvements and deteriorations separately, and various studies have shown that these do not need to be the same[3]. Typically, Wolfe, *et al* determine "real important differences" instead of "real important changes" as they perform a cross-sectional analysis. Intuitively, one would say that the magnitude of "important differences" will be the same as magnitudes of "important changes." The example of total joint replacement shows that this is not true. In addition, the fact that minimally clinically important change (MCIC) for improvement and MCIC for deterioration sometimes differ, clearly implies that "important differences" are not the same as "important changes." Note that this holds for both MCID and RID.

Wolfe, *et al* state that "When applied to RCT, it is not always clear whether MCID should refer to absolute change from baseline or if one should subtract the result of placebo or comparator treatment." Often in RCT differences in change in different arms are determined. Using MCIC, one might report the percentage of patients showing a change larger than the MCIC value in each treatment arm (success rate), and analyze whether these percentages differ significantly between the arms. For RID, Wolfe, *et al* propose to express the results in percentage of RID achieved in each arm. Also in this case one should take the decision to refer to absolute change from baseline or subtract the result of placebo or comparator treatment.

Wolfe, *et al* state that "MCID does not offer clinicians an appropriate goal for improvement, based on patient's perceptions of realistic and desirable HAQ-DI or SF-36 PCS scores." We do not agree with this statement. In our opinion, MCID and MCIC values are far more realistic than RID values. One important point is that the large differences reported in this cross-sectional study may not be attainable (any more) for most patients thinking about improvement. This is illustrated by the fact that Wolfe, *et al* suggest expression of the change as a percentage of RID in RCT and clinical practice.

As a last objection, Wolfe, *et al* state that it is not clear how definitions of MCID should be used to interpret results from RCT or applied to clinical practice. In our opinion the MCID or MCIC defines the boundary between success and failure. The analysis of RCT as described above, com-

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paring the percentages of patients that reach the MCIC or MCID in both treatment arms, is a very realistic approach. The ways in which MCID and RID are applied are the same in this respect.

In summary, in our opinion the RIC is a subclass of MCIC concerning the extreme situation that patients perceive only large changes as minimally important. The OMERACT group[4] has presented a cube with 3 dimensions that are all at issue in this report: a dimension indicating change or difference, a dimension indicating group or individual level, and a dimension indicating the type of difference/change being assessed. In the latter they distinguish minimum potentially detectable, minimum actually detectable beyond error, observed in a population, observed in those estimated to differ/to have changed, and observed in those estimated to have an important difference/change. Information about all these anchors on the scale of a measurement helps to interpret the (change in) scores.

We would plead for rehabilitation of the term MCIC (not MCID) as a change that patients would consider important to reach in their situation, dependent on baseline values or severity of disease, on the type of intervention, and on the duration of the followup period. This MCIC value would be an important parameter to be used in power calculations in the design of clinical studies.

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Dr. Wolfe, *et al* reply

To the Editor:

We would like to address issues raised by de Vet, *et al*. We must first note that in many areas of contention they have inferred uses, methods, and conclusions regarding MCID and RID that we neither suggested nor intended in our article.

We have no argument with the authors' preferences for the term MCIC; however, we would point out that Medline and Google Scholar searches for the abbreviated and unabbreviated term produced 22 MCIC citations compared with more than 500 citations for MCID. When we described meaningful change as MCID or the minimal detectable improvement perceptible to patients we were not endorsing the terminology, but were using inclusive terms that had considerable prior use and that might be understood by readers.

We did not suggest the conjunction of grouped data and patient level data. In fact, we have recently warned against the use of grouped data at the patient level[1]. Instead, we suggested standards and measuring posts that were based on grouped data that could be used in understanding grouped data results that come from clinical trials. In these recommendations the standard deviations of the HAQ/SF-36 are immaterial.

De Vet, *et al* have problems with our application of between-patient differences seen in observational data to within-patients changes observed in clinical trials. We have no such problem, as our purpose was only to describe endpoints that might be used to interpret clinical trials; endpoints such as work disability and total joint replacement are crucial in rheumatoid arthritis (RA) but can never be observed in clinical trials because of the length of time required to reach such endpoints. Where de Vet, *et al* see inconsistencies in results, we see examples that provide clinical guidance, an approach to clinical outcomes that adds meaning to statistical differences and change.

The thesis of de Vet, *et al* that MCIC should represent "change that patients would consider important to reach [and is] dependent on baseline values or severity of disease, on the type of intervention, and on the duration of the followup period," is one with which we agree. The authors have stated this more clearly elsewhere[2]: "The MCIC should not be considered as a fixed value, ...the exact value for the MCIC can be determined, taking into account the aim of the measurement, the initial scores, the target population and the method used to assess MCIC." The problem with this representation, however, is that there is only one known MCID/MCIC for the HAQ (or SF-36) in RA, a value that does not account for baseline values. We are unaware of any current method in RA to determine the proper MCID/MCIC for HAQ/SF-36 that incorporates baseline values or disease severity.

A signal problem with the MCID concept as it applies to functional measurements in RA is not only that the functional outcomes are longterm and beyond the scope of a clinical trial, but that they cannot be measured in the HAQ or SF-36 units of the clinical trial. Instead, the outcomes of interest are work disability, total joint replacement, impoverishment, and mortality. The differences in rates of these outcomes that we have described serve to put into a clinically useful perspective changes that are reported in clinical trials because they allow changes to be placed into the perspective of clinically useful outcomes. In addition, our data address the most important aspect of RA outcome, functional status, rather than change in status. A HAQ change of 0.25 may represent a MCIC for the patient with a HAQ score of 0.5 as well as for a patient with a HAQ score of 2.5. But no one should mistake the difference between these 2 patients.

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Antibodies to Cyclic Citrullinated Peptides in Psoriatic Arthritis: Do Classification Criteria Affect Study Results?

To the Editor:

We read with interest the article concerning the presence of antibodies to cyclic citrullinated peptides (CCP)[1] and as we are performing a similar study of a population from virtually the same geographical area, we would like to describe our interim data and make some comments.

Our aim is to establish the usefulness of anti-CCP antibodies in discriminating psoriatic arthritis (PsA) and rheumatoid arthritis (RA). Our inclusion criteria were the same as those used by Bogliolo, *et al*[1]: consec-

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utive outpatients with a diagnosis of PsA according to Moll and Wright[2]. As this definition leaves it up to the researcher to decide whether or not to include cases positive for rheumatoid factor (RF), its specificity depends on how patients with RA with concomitant psoriasis are ruled out. In our study, patients with RA with psoriasis and RF-positive patients with true PsA were distinguished on the basis of an expert's opinion. More precisely, the patients with features characteristic of RA (rheumatoid nodules, vasculitis, typical RA radiographic changes) were excluded from the study, whereas RF-positive patients with features characteristic of PsA (dactylitis, distal interphalangeal involvement, axial involvement, and typical PsA radiographic changes) were included. Anti-CCP antibodies were measured in sera using a commercially available second generation ELISA kit (INOVA kit, Quantalite Ltd. San Diego, CA, USA), for which the upper normal limit suggested by the manufacturer is 20 UI/ml.

We have so far enrolled 129 patients with PsA whose main demographic and clinical characteristics are shown in Table 1. At the threshold value of 20 UI/ml, only 4 (3.5%) patients were anti-CCP positive, with serum levels of 32, 43, 126, and 159 UI/ml. Six patients had anti-CCP values of 10-20 UI/ml, and the remaining 119 values were < 10 UI/ml. All anti-CCP positive patients had polyarticular disease, and no correlation was found between the presence and titer of these antibodies and the markers of disease severity (number of irreversibly damaged joints, erosive disease, disability as measured by the Health Assessment Questionnaire, and therapy with disease modifying antirheumatic agents). Interestingly, the 35 patients (27.1%) in our series who were positive for RF (> 20 UI/ml) included the 2 patients with the highest anti-CCP values.

In the study by Bogliolo, *et al*[1], 16 out of 102 (15.7%) patients with PsA were positive for anti-CCP antibodies, a significantly higher percentage than we found ($p \leq 0.001$ by Fisher's exact test). All positive values were > 40 UI/ml, indicating that the large number of positive anti-CCP cases was not due to an exceedingly low normal limit (5 UI/ml). Finally, the median positive anti-CCP value was higher in Bogliolo's study population than ours: > 100 UI/ml versus 84 UI/ml, respectively.

Comparison of the 2 studies reveals significant differences in the number of patients with PsA with a positive anti-CCP test (15.7% vs 3.5%), which is unlikely to have been due to mere chance because the patients were comparable in terms of ethnicity, demographics, the main clinical features (Table 1), and the level of the attended center (both tertiary). There are 2 reasonable explanations: a difference in the sensitivity of the tests and/or the inclusion of patients with RA and concomitant psoriasis. The first possibility cannot be verified (the same sera should be evaluated by both tests) but seems to be quite remote as both studies used second-generation enzyme-linked assays; a misclassification of some patients appears to be much more likely. It has been shown that Moll and Wright's definition of PsA is sensitive and specific when RF-positive cases are excluded[3], but it clearly loses part of its specificity if they are included. Bogliolo, *et al*[1] stated that only 6 out of the 16 anti-CCP positive patients had unmistakable evidence of PsA, while the remaining patients could have had RA coexisting with psoriasis, thus confirming the relative lack of specificity of diagnosis. We used the same diagnostic definition in our study, but also classified the patients as having PsA only if RA could be reasonably ruled out on sound clinical and radiographic grounds. In this regard, as about 27% of the patients were RF positive, our expert considered that this positivity had poor discriminant value. Comparison of the 2 studies seems to indicate that this is a classical case of a difference in inclusion criteria leading to a significant difference in results, which is very important when the sensitivity and specificity of a new test in a specific rheumatic disorder are still unknown.

The main conclusion we can draw is that great attention needs to be paid to diagnostic/classification criteria when performing this kind of study. In the case of PsA, the relative confusion generated by the existence of at least 7 sets of classification criteria[3] should be reduced by the recent proposal of new criteria[4]. Another possible conclusion is that it is indeed virtually impossible to discriminate PsA and RA in a few cases. The coexistence of PsA and RA may have played a role but only in a few cases because, given the approximately 1% prevalence of RA, mere chance would have meant that only one of Bogliolo's 102 patients with PsA should have had coexisting RA. Finally, whether anti-CCP antibodies will be as helpful in predicting disease severity in PsA as in RA[5] will depend on their true frequency in PsA.

Table 1. Main demographic and clinical characteristics of 129 study patients with PsA. Values are number of patients (%), unless otherwise indicated.

Variable	
Median age, yrs (mean ± SEM)	54 (54 ± 1.4)
Median arthritis duration, yrs (mean ± SEM)	11 (12.3 ± 1)
Median psoriasis duration, yrs (mean ± SEM)	16 (18 ± 1.3)
Males/females	81/48
Mono-oligoarthritis	43 (33)
Polyarthritis	83 (64)
Axial predominant	2 (2.5)
Exclusive DIP involvement	1 (1.2)
Mutilans	11 (8.7)
Axial involvement (all patients)	62 (48.1)
Dactylitis	62 (48.7)
Enthesitis	36 (28)
Damaged joints (mean ± SEM)	3 (5.3 ± 0.9)
Erosive arthritis	100 (77.8)
DMARD therapy	78 (60)
RF positive	35 (26)
CCP positive (> 20 U/ml)	4 (3.1)
CCP median value, U/ml (mean ± SEM)	4.5 (7.9 ± 1.5)

DIP: distal interphalangeal; DMARD: disease modifying antirheumatic drug.

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Dr. Bogliolo, *et al* reply

To the Editor:

We are grateful to Dr. Marchesoni and colleagues for their interest in our study and for their data so nicely reported. We think some additional comments are required to compare results of the 2 studies.

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First of all the aims of the studies are different: while Marchesoni, *et al* try to establish the usefulness of anti-cyclic citrullinated peptide (CCP) antibodies in discriminating psoriatic arthritis (PsA) and rheumatoid arthritis (RA), our study[1] focused on the clinical characterization of anti-CCP positive patients with PsA.

As stated[1], we included in our study all patients with idiopathic arthritis and psoriasis, according to Moll and Wright[2], without any additional exclusion criteria. Of course, a number of patients with RA and psoriasis may have been included[3]. However we think that a single expert's opinion may be questionable as an inclusion/exclusion criterion and may be less reproducible than a definite set of criteria[4]. We agree with Dr. Marchesoni in that patients with clear clinical and radiographic evidence of RA do have RA; however, some patients may present with signs and symptoms typical of both disorders. Moreover, since the anti-CCP assay has become very popular, we wonder how the expert's opinion might have been influenced by a positive test for anti-CCP.

Dr. Marchesoni and colleagues state that Moll and Wright's classification has proven to be sensitive and specific when RF positive cases are excluded; however RF positivity was considered to have poor discriminating value in their study. Surprisingly enough, their approach in determining true PsA, based on their expert ruling out RA, led to the highest frequency of RF positive patients reported in PsA so far[1,5].

It would be interesting to know how many patients fulfilling Moll and Wright's criteria were excluded, as well as the clinical picture and autoantibody profile of these patients. A careful analysis of these patients might be useful to support the need for the expert's opinion as an additional criterion and the usefulness of anti-CCP antibodies, rather than RF, in discriminating PsA and RA.

We hope the efforts of Dr. Marchesoni will lead to a suitable set of true diagnostic criteria for PsA in the near future[6]. At present, however, we think that a pragmatic approach to the selection of patients for clinical studies involves looking for prognostic factors (and we feel that anti-CCP antibodies may be among them) according to widely accepted classification criteria, particularly as therapeutic strategies in poor-prognosis PsA and RA are quite similar[7].

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Use of Statistical Analysis in Open Extension Studies

To the Editor:

We read the article by Genovese, *et al*[1] with interest. We were surprised that "no formal statistical comparisons were made among the original 3 treatment groups because of the observational design of the extension and the fact that the patients' decision to enter the extension was not likely to be a random event." We believe this matter deserves more discussion.

This paper[1] reported a 4-year open experience with 25 mg etanercept twice a week after a blinded protocol of 10 and 25 mg compared to solo weekly methotrexate (MTX)[2]. There was another report about the one-year outcome, after the blind phase had ended, of a randomized trial[3]. This report included formal statistics concerning the data. Do the authors suggest that the conclusions in the one previous article were flawed?

Fortunately this probably was not the case. We rather think the authors' current statement about randomization being a prerequisite for sound statistics is incorrect.

Of course, the authors are correct that data concerning why some patients chose to participate and others chose not to participate are not fully available. Nonetheless, concern about bias in different study groups should not dictate non-performance of statistical analyses, in our opinion. Indeed, such analyses may help elucidate any bias and help determine whether we may be dealing with a non-random phenomenon.

Safety data given in Table 2[1] suggest that the initial MTX group had the lowest number of adverse effects. Provision of formal statistical analyses might have helped readers to determine whether these differences might be explained by differences in patient status at baseline, which might have led to conclusions that differed from those of the authors.

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Dr. Genovese, *et al* reply

To the Editor:

We thank the Drs. Yazici for their response to our article[1] and believe that it offers an excellent forum for understanding the appropriate use of statistical analysis in randomized clinical trials that cross over into longterm observational studies.

In the 2-year article[2] patients had been randomized and remained on their original treatment assignments for the duration of the 2 years. The blind for the study was broken during year 2, but on average patients remained blinded for 18.4 months and this study had very low attrition. Safety and efficacy outcomes were compared between the 3 groups utilizing statistical tests for significance. This was feasible and appropriate because all groups continued to receive treatment according to random assignment, and, more important-

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ly, all subjects who received any active drug were included in the analysis. The analysis in this study used the last observation carried forward (LOCF) technique to account for missing data and early drop-outs.

The formal longterm extension study began when each patient completed year 2. In this observational study, all interested subjects were allowed to receive etanercept at the 25 mg biweekly dose, with the use of methotrexate (MTX) and corticosteroids determined by the investigator based on disease activity. The decision to enter the extension was certainly subject to a number of biases. Formal statistical significance testing was not performed in this study for several reasons: (1) differential drop-out rates were likely to bias results due to confounding by indication; (2) there was an increasing amount of heterogeneity of treatment within each group as other medication changes were made according to disease activity; and (3) the safety analysis focusing on the use of etanercept examined all patients who received at least 1 dose of etanercept, and excluded patients from the MTX arm who did not enter into the etanercept only phase of the study.

Table 2[1] shows the safety data for all patients who received at least one dose of etanercept. Careful examination of subjects included in this portion of safety analysis shows that only 143 of the original 217 subjects (66%) randomized to the MTX arm received any etanercept due to early termination from the original phase of the study or elected not to participate in the longterm extension. In comparison, all subjects originally assigned to receive either dose of etanercept (208/208 of 25 mg etanercept and 207/207 of 10 mg etanercept) are included in the safety analysis. So although it appears that there may be fewer adverse events in the original MTX arm, fewer subjects were included. Many of the adverse events seen in the early phases of the study in subjects receiving MTX without etanercept were not evaluated in the analysis of safety in subjects receiving etanercept. Inferential statistics in this instance would be inappropriate because one arm is deliberately left-censored. The 3 groups in comparison were not equal with respect to length of time receiving etanercept or with period of time under study. We were concerned that the inclusion of formal statistics would not only be unable to uncover any inherent biases, but would lead to misinterpretations of the data. In fact the application of statistical analysis in this situation would ignore or obscure the fact these significant biases exist and would legitimize this type of analysis in the eyes of many readers. While testing for statistical significance is very important in evaluating study results, careful attention to the composition of each group and the clinical significance of the measured outcomes should not be ignored in the absence of p values.

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Macrophage Activation Syndrome as an Early Presentation of Lupus

To the Editor:

We describe the occurrence of macrophage activation syndrome (MAS) as a presenting feature of childhood systemic lupus erythematosus (SLE). MAS, a life-threatening complication of systemic inflammatory disorders, can be difficult to diagnose, despite recognized clinical features[1]. MAS associated with lupus is rare in pediatrics, with only one other case reported within a series of 24 children[2].

A 10-year-old girl from Yemen presented with a 6 week history of persistent fevers (up to 40°C) and rigors, preceded by 4 months' weight loss, anorexia, and lethargy. Questioning revealed symptoms of alopecia, swollen glands, headaches, and diarrhea. Infection screening was negative, and fever was unresponsive to antipyretics or broad-spectrum antibiotics. She was acutely unwell, cachexic, clinically anemic, and had a gallop rhythm, soft systolic murmur (from hyperdynamic circulation and anemia), bilateral periorbital edema, and hepatosplenomegaly. She developed sudden loss of right-side vision over a period of a few hours.

Investigations showed pancytopenia (hemoglobin 5.5 g/dl, white cell count 0.9×10^9/l, platelet count 40×10^9/l), positive antinuclear antibodies (ANA; 1:2560) and anti-dsDNA (25.9 IU/ml; normal < 9.9), and negative anti-ENA antibodies. Despite a normal bone marrow locally, a repeat aspirate revealed active hemophagocytosis. Diagnosis of MAS was supported by high lactate dehydrogenase (LDH; 1289–2343 U/l), high ferritin (1589–2087 μg/l), low fibrinogen (1.0 g/l), low platelet count (40×10^9/l), and relatively low erythrocyte sedimentation rate (ESR; 30–65 mm/h) disproportionate to the clinical picture (Table 1).

The American Rheumatism Association criteria of lupus were met by evidence of nephritis (urine albumin/creatinine ratio 77.8 mg/mmol (normal 0.7–7.4), with cellular casts on microscopy, and calculated glomerular filtration rate of 50 ml/min/1.73 m^2), cytopenia, positive immunoserology, positive ANA, and positive antiphospholipid antibodies [aPL; anticardiolipin IgG 32.6 U/ml (normal 0–17 U/ml)]. Anti-ß$_2$-glycoprotein and antiprothrombin were not available. Lupus anticoagulant testing was negative by dilute Russell viper venom time. Diagnosis was supported by low complement C3 (0.23 g/l; normal 0.75–1.65), C4 (0.07 g/l; normal 0.14–0.54), and normal C-reactive protein. Renal biopsy (taken 3 weeks after aggressive treatment) showed glomerular deposition of C1q and C3 on immunohistochemical staining, with mesangial and subepithelial deposits on electron microscopy, consistent with WHO class 2 lupus nephritis.

Initial treatment was dexamethasone 10 mg/m^2/day (equivalent to 53 mg/day prednisolone), without improvement. Following a rheumatology referral, her steroid regime was changed to our usual practice of 30 mg/kg/day intravenous methylprednisolone (equivalent to 480 mg prednisolone/day) for 3 consecutive days, repeated 1 week later, with daily prednisolone maintenance. She remained extremely unwell and was given further methylprednisolone, together with plasma exchange and intravenous cyclophosphamide (500 mg/m^2; National Institutes of Health regime for 6 months, with accelerated dosing at onset). Aspirin was started owing to positive aPL.

Right side central retinal artery and vein occlusion was identified by ophthalmologic examination and magnetic resonance image scan (angio-

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Table 1. Investigation results over time related to clinical course (dates shown on top line).

Clinical Event/ Investigation	Normal Range	Dec 2 Bone marrow. Loss of vision R eye	Dec 9 Blood & plt given	Dec 12 Dex started. 2nd bone marrow. Blood given	Dec 15 Dex Day 4	Dec 16 IV MP Day 1 Pan-creatitis. Plt given	Dec 18 IV MP Day 3. Bleed. Plas Ex	Dec 19 Plas Ex. CYC dose 1	Dec 23 Plas Ex Day 5	Dec 24 Next course of IV MP given	Dec 27	Jan 2 Line sepsis	Jan 6 Renal Bx	Jan 8 CYC dose 2	Jan 19	Jan 30 CYC dose 3
Hb	11.5–15.5 g/dl	7.5	5.5	8.9	10.4	9.3	6	12.2	8.4	7.9	10.5	10	9.4	10.7	9.3	9.6
WCC	4.5–13.5 × 10^9/l	1.6	0.89	1.8	3.94	6.09	10.39	11.18	5.65	5.09	1.96	1.22	5.39	6.05	10.49	17.84
Neutrophils	1.5–8.0 × 10^9/l	0.8	0.59	0.92	2.28	4.74	8.61	9.22	4.85	4.38	1.46	0.54	3.9	4.26	8.02	13.02
Lymphocytes	1.5–7.0 × 10^9/l	0.6	0.23	0.67	0.82	0.68	0.64	0.96	0.52	0.51	0.32	0.19	0.75	0.87	1.52	2.14
Platelets	150–450 × 10^9/l	83	40	70	45	49	120	92	53	52	72	127	131	112	260	291
ESR	0–10 mm/h	31		40		35	80		8	3		65		30		
CRP	< 20 mg/l	< 7	< 7		< 7						8	38	37			< 7
PT	9.9–12.5 s		11.4	11	12.5			15.5		11.8					10.3	
APTT	26–38 s		47.2	45.1	33.4			34.8		37.8					33.2	
Thrombin	9.2–15.0 s		18.6	16.4	19			19.2		11.2					11.7	
Fibrinogen	1.7–4.0 g/l		1.1	1.4	1			0.7		1.6					3.6	
Ferritin	7–150 μg/l	2087				1589										
Urea	2.5–6.0 mmol/l	1.8	4.7	4.3	11.6	10	10.4	10.8	16	16.8	14.4	5.5	5.4	6.8	8.9	8.6
Creatinine	35–70 μmol/l	51	54	59	79	65	72	59	51	44	48	36	34	36	39	38
ALP	130–560 U/l	123	119	111	82	83	71	37	33	33	49	59	6	8	75	86
ALT	10–35 U/l	44	54	49	33	29	26	23	22	18	7	28	73	36	28	24
Amylase	30–100 U/l	27				1020	207	118	98	85		62		76	84	61
Lipase	13–150 IU/l					> 10000	1280	915	779	640		354			150	79
LDH	380–770 U/l	1289	2343													

Dex: dexamethasone, CYC: cyclophosphamide, Plas Ex: plasma exchange, IV MP: intravenous methylprednisolone, plt: platelet transfusion, Bx: biopsy, Hb: hemoglobin, WCC: white blood cell count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PT: prothrombin time, APTT: activated partial thromboplastin time, LDH: lactate dehydrogenase.

graphy and Doppler imaging were unavailable). Thrombophilia screening was unremarkable, and rate of funduscopy improvement over time was thought to be consistent with vasculitis rather than thrombosis, so warfarin was not given. Right side blindness persisted, possibly secondary to neuronal damage.

The clinical course was complicated by acute pancreatitis (diagnosed by computer tomography scan plus elevated amylase and lipase), a recognized complication of SLE[3]. She responded to conservative treatment with antibiotics, steroid, octreotide, and total parenteral nutrition.

MAS represents clinical and laboratory features mediated by cytokine overproduction from excessive activation and proliferation of well differentiated macrophages (histiocytes)[1,4]. The striking bone marrow appearance has led to the term "reactive hemophagocytic lymphohistiocytosis" (HLH) among hematology-oncology investigators[4].

Detection of MAS secondary to lupus is complicated, since many features are common to both pathologies, such as fever, pancytopenia, leukopenia, lymphadenopathy, neurological manifestations, arthritis, rash, hepatomegaly, renal or cardiac manifestations, and increased LDH. However, hallmark features of MAS include hyperferritinemia, hypofibrinoginemia, liver dysfunction with hypertriglyceridemia and raised liver enzymes, splenomegaly, and bone marrow aspirate showing active hemophagocytosis. A paradoxically low ESR (secondary to hypofibrinoginemia) in a patient is suggestive[1,2,5]. Lupus patients with pancytopenia should have a bone marrow biopsy to exclude MAS. An infection screen is also necessary, but frequently negative, suggesting lupus related immune changes as a cause of MAS[5].

It is crucial to recognize and treat MAS promptly with immunosuppression, and where appropriate, treatment of infection and removal of triggering medications[2]. There are no agreed protocols, but primary treatment involves parenteral administration of high-dose corticosteroids with supportive management of fluid balance and coagulopathy[1,2,6]. Other reported therapies (most commonly used in conjunction with steroid) include cyclosporin A, etoposide, intravenous immunoglobulins, cyclophosphamide, plasma exchange, and etanercept[1,2,6]. Etoposide can induce bone marrow aplasia, and there was reluctance to use cyclosporine due to renal impairment in this case[6]. Cyclophosphamide is a recognized treatment of severe lupus, and was felt to be most appropriate. In view of its delayed action, with a 10-day nadir, plasma exchange was also used.

The combination of methylprednisolone, plasma exchange, and cyclophosphamide led to resolution of MAS. This case illustrates the importance of considering the underlying diagnosis when directing treatment, to halt stimulation of macrophages and prevent mortality.

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Corrections

Tannenbaum H, Bombardier C, Davis P, Russell AS. An evidence-based approach to prescribing nonsteroidal antiinflammatory drugs. Third Canadian Consensus Conference. J Rheuamtol 2006;33:140-57. The penultimate sentence of the "Lumiracoxib" section on page 143 should read: "Importantly, however, taking ASA largely negated the GI benefits of lumiracoxib, with reduction in complications by [not "to"] only 21%." We regret the error.

Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005;32:2485-7. Author's name George Bruyn should be George A.W. Bruyn. We regret the error.

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