

Correspondence



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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Patient's Ethnicity and Use of Therapies in Rheumatoid Arthritis

To the Editor:

We welcome the findings by Ang, *et al*¹, who observed that patient's ethnicity does not influence utilization of effective therapies (biologic agents and disease modifying drugs) for treatment of rheumatoid arthritis. Nevertheless, we would caution against complacency in the light of these findings.

One issue that has recently drawn attention is that of patient education, including patient information for ethnic groups with a first language other than English². Perhaps understandably, the difficulty and additional time requirement of explaining a treatment (with or without an interpreter) may lead the healthcare practitioner to make precipitant assumptions or even decisions on behalf of such patients. Therapies like biological agents requiring in-depth and often complex discussions about risk-benefit can put added pressure on the interaction between healthcare professional and patient.

Some healthcare practitioners working in hospitals with ethnically diverse patient populations have indicated that they sometimes delay or even decline to offer such patients a biologic agent if they are unsure whether the patient has adequately understood the risk-benefit of such therapies. Communicating the issue of longterm, unknown side effects of biologic agents to the patient is of particular concern.

While we recognize that such approaches are usually well meaning, we believe that all reasonable attempts should be made to ensure that patients who do not speak English be given every opportunity to commence these therapies. Although the use of interpreters and written material in other languages has limitations and disadvantages, we believe that these are areas requiring further research and healthcare investment.

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Dr. Ang, *et al* reply

To the Editor:

We thank Dr. Adebajo and Dr. Mitchell for their interest in our article¹. As we emphasized, 97% of the patients analyzed had some type of medical insurance, and they were seen in the setting of private rheumatology care. With these caveats, our study suggested that patient's ethnicity does not influence utilization of effective therapies in rheumatoid arthritis. However, we recognize that ethnic disparity may still exist in uninsured patients who are appropriate candidates for biologics but have not yet received such effective therapy. By virtue of its inclusion criteria, the RADIUS study¹ cannot address such possibility.

Ethnic disparities in healthcare in the United States have prompted speculation about the role of the physician as a contributory factor in these disparities^{2,3}. Given that some physicians consider "non-English-speaking" as an undesirable patient characteristic⁴, it is easy to speculate that patients who do not have English as their first language might receive substandard care. For instance, a physician may be reluctant to expend extra effort to explain the risk and benefits of a procedure or an expensive drug (e.g., biological agent) to a "non-English-speaking" patient. Although such hypothesis is provocative and has some support from the literature⁵, current evidence is insufficient to permit a definitive conclusion that physician biases are responsible for disparities in the use of healthcare products and services⁶. Clearly, more study is needed to evaluate the role of the physician in the causation of healthcare disparities. Our study suggests that patients with equivalent insurance status are treated similarly by rheumatologists, regardless of ethnicity.

Nonetheless, we agree with Adebajo and Mitchell on the importance of providing culturally congruent patient and family education. The success of culture-specific education in areas such as diabetes care and cancer screening cannot be underestimated^{7,8}.

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Juvenile Idiopathic Arthritis Classification Criteria: Loopholes and Diagnosis Software

To the Editor:

We are writing in response to the article by Merino, *et al* regarding an evaluation of the revised International League of Associations for Rheumatology (ILAR) criteria for classification of juvenile idiopathic arthritis (JIA)¹. In our clinic we have been attempting to use the ILAR classification scheme as a replacement for the outdated American College of Rheumatology criteria for juvenile rheumatoid arthritis. In the process we have uncovered some logistical problems with the ILAR scheme². The first issue is with exclusion (a), which deals with psoriasis. Under the current scheme, a patient who has arthritis without psoriasis, but accompanied by both dactylitis and nail pitting, poses a problem. One would like to give the diagnosis of psoriatic arthritis, since this patient would meet the criteria under the ILAR scheme. However, since by the mere fact that this patient has arthritis, he or she also meets criteria for either oligo- or polyarthritis. Since the (a) exclusion does not exclude this patient without psoriasis, we must give a diagnosis of undifferentiated arthritis, since 2 diagnostic criteria are now met, despite the fact that this does not seem to be within the spirit of the classification scheme. The simple solution to this problem is to change the wording of exclusion (a) to also include the term "psoriatic arthritis." This is in parallel with the logic of exclusions (c) and (e), which prevent similar logical conundrums for enthesitis related arthritis (ERA) and systemic arthritis, respectively.

The second issue with the scheme also deals with the application of the exclusions. In instances where a patient may meet criteria for 2 categories, but where the exclusions would prevent such a circumstance, it is not explicit how these situations should be handled. An example will illustrate this point: a patient who meets criteria for systemic arthritis but who also has enthesitis becomes difficult to classify. If we first apply the criteria for systemic arthritis, we find the patient satisfies the diagnosis, and thus exclusion (e) prevents the diagnosis of ERA being applied. Alternatively, since the patient has arthritis and enthesitis, he or she satisfies the diagnosis of ERA, and thus exclusion (c) prevents the diagnosis of systemic arthritis. Thus, the order in which the criteria are applied changes the final diagnosis given. It is unclear whether these situations are to be given the diagnosis of undifferentiated arthritis, or whether there needs to be an "order of operations" for applying the criteria. We propose that the criteria should be applied in the order written in the original article describing the ILAR scheme: systemic, oligo, poly, psoriatic, and lastly, ERA. Thus, the patient in the example above would still be classified as systemic arthritis. This prevents unnecessary placement of patients in the undifferentiated category. Further, with the changes to exclusion (a) outlined above, these changes would not cause enthesitis to disallow the diagnosis of psoriatic arthritis as it currently does. Enthesitis is a well documented feature of patients with psoriatic arthritis³, and we believe it should not exclude the diagnosis, even if it is not part of the diagnostic criteria. We believe these simple modifications to the classification criteria will help to clarify the appropriate diagnostic category for children with JIA, and will help to lower the rate of diagnosis of undifferentiated arthritis in children.

The need for internal logistical consistency within the ILAR classification scheme for JIA is important to ensure that we all are applying the criteria equally. Clearly, application of the ILAR scheme, even as carefully

constructed as it is, can be difficult and cumbersome. In order to facilitate accurate use of the criteria, we have developed a computer instrument, the "JIA Calculator," which automates the logical process of determining a diagnosis. To develop such an algorithmic way of arriving at a diagnosis, we had to revise the ILAR criteria to be internally logically consistent, as outlined above. Our hope is that this tool will speed the process of arriving at the appropriate diagnosis, while ensuring correct application of the diagnostic criteria. We have made the JIA Calculator available at the following URL: <http://www.jra-research.org/JIACalc/> [accessed October 11, 2006]. This should support all those in clinical research studies of children with JIA. We welcome any feedback that would improve this instrument for the benefit of the rheumatology community in general.

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Dr. Merino, *et al* reply

To the Editor:

We read with great interest the comments by Behrens, *et al* on the latest JIA classification criteria¹. It should be kept in mind that the ILAR classification represents an effort to develop internationally accepted criteria that enable identification of homogeneous groups of children with chronic arthritis. The ILAR criteria have obvious limitations, classifying children with defined psoriatic arthritis or systemic arthritis into the undifferentiated arthritis category (for details see Table 2 of our study²). It is also well known that the ILAR classification includes strict criteria to differentiate enthesitis related arthritis from psoriatic arthritis, despite the classical inclusion of psoriatic arthritis within the HLA-B27 associated diseases³. Therefore, we do not believe that substitution of exclusion (a) (Psoriasis or a history of psoriasis in the patient or first-degree relative) with "the presence of psoriatic arthritis," as proposed by Behrens, *et al*, will improve the homogeneity of the classification, although it would probably classify more patients.

In regard to classification of systemic arthritis, it usually does not present a problem, being easily differentiated from other categories of JIA. The case mentioned by Behrens, *et al*, a child with enthesitis and systemic features, is extremely unusual. On the other hand, imaging methods such as ultrasound are not frequently used in the evaluation of enthesitis in pediatric patients.

All chronic pediatric arthritis classification systems based on clinical features and scores will lack specificity, and the introduction of small changes will not increase their performance significantly. The way forward leads toward incorporation of specific biomarkers into the classification systems, whenever they become available^{4,5}.

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Carcinomas in Patients with Systemic Lupus Erythematosus

To the Editor:

We read with interest the article by Bernatsky, *et al*, "Cancer screening in patients with systemic lupus erythematosus [SLE]"¹. We share their views on the necessity of screening studies in patients with SLE to enable early detection of malignant conditions. Concurrent malignancy in SLE patients is a serious problem that may affect the course of the autoimmune disease, the methods of treatment of the carcinomas, and the possible complications of this treatment.

We present the case of a 30-year-old woman diagnosed 20 years ago with SLE with skin, joint, blood, nerve, and kidney involvement. She received multiple pulse therapy with cyclophosphamide and methylprednisolone. The maintenance therapy in the past year was prednisolone 10 mg/day. During screening study and mammography, she was found to have tumor of the right mammary gland. During surgery, this was further specified as intraductal carcinoma with focal invasive changes and no metastases in the lymph nodes. After an organ-preserving surgery, she received radiation therapy with an alternative exposure dose of 50 Gy. Although the dose was reduced, she developed a severe bullous dermatitis. A late complication of the radiation therapy was subcutaneous tissue fibrosis in the exposure area.

Immediately after radiation therapy, we found indications of SLE activity — photosensitive rash on the face and neck, arthralgia, myalgia, edemas in the eyelids and shanks. Immunological studies revealed antinuclear antibodies at the titer of 1:320. She was positive for antibodies to the Sm and Ro/SSA antigens (transiently negative). Proteinuria was as high as 3.2 g/24 h. The pulse therapy with methylprednisolone in a dose of 750 mg on 3 consecutive days led to clinical and immunological remission. She continued receiving maintenance therapy with prednisolone (15 mg/day), chloroquine (250 mg/day), and tamoxifen (40 mg/day). She is going to have bilateral ovariectomy because polychemotherapy is contraindicated for her.

It is well known that patients with systemic diseases of the connective

tissue (SLE in particular) are at a higher risk of developing carcinomas of different localizations. The most prevalent malignancies are breast carcinomas, carcinomas of the skin and cervix of uterus, and hemopoiesis^{2,3}. For some age groups there are screening programs for early diagnosis of carcinomas. Our SLE patient with carcinoma is 30 years old and cannot be categorized as belonging to these groups^{3,4}. Besides the known risk factors for developing carcinomas of the breast, other factors undoubtedly have a role in patients with SLE, such as treatment with cytostatic drugs (alkylating agents) and genetic factors (bearing on the estrogen receptors, estrogens, and their metabolism)⁴.

By reporting this case we would draw attention to the therapeutic problems in patients with SLE and carcinomas. The treatment of the autoimmune disease has its limitations, with limited possibilities for radiation therapy and chemotherapy. The issue about the frequency of subsequent complications remains controversial. Our patient developed a postradiation bullous dermatitis and a late complication of fibrosis of the subcutaneous tissue.

Some authors contend that toxicity after radiotherapy in patients with SLE and carcinomas does not exceed the complications in other groups of patients⁵. We support the view of others that patients with SLE show increased toxicity after radiation therapy⁶⁻⁸. The systemic character of the disease and the changes in the immune system determine the poorer tolerance of radiation compared with patients without collagen diseases.

There is no doubt that screening studies are necessary for early detection of carcinomas in patients with SLE. It is only an early diagnosis that can provide an early treatment simultaneously with control of the activity of the autoimmune disease.

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Dr. Bernatsky, *et al* reply

To the Editor:

The letter of Dr. Panchovska and colleagues indicates appropriate concern regarding their young patient who developed invasive breast carcinoma. However, we must caution against any misinterpretation of our previous

work regarding cancer in SLE. First, the across-country estimate for breast cancer from our international multicenter study did not actually suggest an overall increased incidence of breast cancer; our estimated standardized incidence ratio (ratio of observed cancers to those expected) was 0.8 (95% CI 0.6, 1.0)¹. Regarding the suggestion of Dr. Panchovska that genetic factors related to estrogen receptors and metabolism may be important in terms of mediating breast cancer risk in SLE, we know of no existing clinical data in this regard. No doubt estrogen exposures have some influence on breast cancer risk in SLE, but how this might occur is completely unknown. We would point out that women with SLE in many cases may have lower endogenous or exogenous estrogen exposures². However, we admit to a certain inhomogeneity of the risk estimates for hormone-sensitive cancers in previously published single-center SLE cohort studies, which likely suggests a complex interplay of risk factors.

Given some evidence suggesting that cancer cases in SLE may lead to a lower than expected survival³, we are concerned at Dr. Panchovska's suggestion that patients with autoimmune disease have "limited possibilities for radiation therapy and chemotherapy." From our perspective, SLE patients who are diagnosed with a malignancy should, if at all possible, be afforded the same treatment options as persons without SLE. We draw attention again to the work of the late Veronique Benk, a tireless advocate for excellence in oncology care, whose work has shown that some therapeutic measures may be inappropriately withheld from patients with SLE who develop cancer⁴. Although the patient Dr. Panchovska describes did unfortunately suffer a severe reaction from radiation, it is rarely advisable to base one's conclusions on anecdotal experience; thus we are wary of Dr. Panchovska's assertion that "patients with SLE show increased toxicity after radiation therapy." Again, a major concern of ours is that appropriate therapeutic options not be denied to our patients. To date, the reviews and small case-control studies have rarely supported an increase in acute radiation reactions in most SLE patients⁴⁻⁸. Admittedly, patients with skin involvement due to the distinct entities of scleroderma or discoid lupus may be more sensitive to radiation-induced skin complications, as several have suggested⁹⁻¹⁴. However, this is in contrast to the reported experience for the general SLE population, although we admit that some controversy is still apparent¹⁵⁻¹⁹, and that there may be some biologic plausibility for increased reactivity to radiation therapy in SLE, given the prevalence of photosensitivity in this population²⁰.

One issue we can agree on wholeheartedly is that efforts must be made to ensure that individuals with SLE undergo cancer screening according to recommended guidelines. This is likely particularly important for cervical dysplasia, which occurs with increased frequency in SLE. Thus, special care should be taken to ensure that cancer screening is not neglected, particularly in SLE patients with a history of dysplasia, or who are undergoing immunosuppressive therapy, which increases the risk of cervical dysplasia.

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Neurological Complications of Infliximab

To the Editor:

In a recent case report¹, Jarand, *et al* consider the diagnosis of progressive multifocal leukoencephalopathy (PML) in their patient with apparent demyelination following treatment with infliximab (Case 1). As this diagnosis entails a very poor prognosis, it is important to rule out active infection with the causative agent — JC virus — at an early stage. This cannot be done on magnetic resonance imaging (MRI) evidence alone.

Although PML lesions usually appear hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, it was recently reported that PML can present atypically on MRI as a ring-enhancing lesion with mass effect².

The diagnosis is readily missed³ and has probably been underreported as a complication of treatment with anti-tumor necrosis factor- α (TNF- α) agents⁴: in 18 cases of apparent demyelination reported to the US Food and Drug Administration following treatment with etanercept or infliximab, brain biopsy was performed in only two⁵. Histopathology — the definitive way of establishing a diagnosis of PML — was consistent with encephalopathy rather than demyelination in one of these 2 brains. Furthermore, that patient's symptoms and progressive lesions on MRI were in keeping with PML rather than multiple sclerosis⁶.

Corroborative evidence that anti-TNF- α therapy may predispose to PML also comes from experience with natalizumab, a recombinant humanized antibody directed to the α_4 integrin molecule. Use of this agent was suspended last year after it was associated with a number of cases of PML³. Genain, *et al*⁷ found retrospectively that the number of T cells, and in particular regulatory T cells, was profoundly depleted in those patients who developed PML following treatment with natalizumab (< 0.2% compared to healthy control, levels of 1–4%). This suggests that T cell lymphopenia may account for the increased risk of PML infection seen in patients taking natalizumab. Wachi, *et al*⁸ recently described a similar depletion of T cells following treatment with infliximab, suggesting a possible mechanism for how anti-TNF- α therapy may predispose patients to JC virus infection and PML.

We recommend that any patient presenting with new central nervous system symptoms following treatment with anti-TNF- α agents be evaluated for JC virus infection by polymerase chain reaction on cerebrospinal fluid. This test is more than 90% sensitive and almost 100% specific⁹ but should be used in conjunction with MRI to rule out PML. The wait-and-see approach adopted by Jarand, *et al* is suboptimal when potentially dealing with a rapidly fatal disease. Early detection is critical.

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Andrew Ostor has received honoraria and grants for attending meetings from Schering-Plough and Abbott Immunology.

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To the Editor:

I read with interest the article by Jarand and colleagues on neurological complications of infliximab¹. The article described 3 patients with rheumatoid arthritis who developed peripheral neuropathy during their treatment with infliximab.

Anti-tumor necrosis factor (anti-TNF) agents have been extensively used in recent years for the treatment of various inflammatory diseases such as rheumatoid or seronegative arthritis, Crohn's disease, psoriasis, or vasculitides. Therapy with these agents has been associated with several side effects including hypersensitivity reactions, infections, lupus-like syndromes, and, rarely, demyelinating diseases.

The presence of polyneuropathy in association with infliximab treatment has also been described in other previously published cases²⁻⁴, not mentioned by this article¹. In most of these cases, neurological symptoms were compatible with multifocal motor neuropathy (MMN) with conduction block. MMN is an immune-mediated demyelinating neuropathy characterized by progressive asymmetrical weakness of the limbs in the absence of sensory involvement. Recently, we reported 2 additional cases with peripheral neuropathy, which occurred during infliximab treatment, one with MMN and another with axonal sensory polyneuropathy, reversed upon discontinuation of the drug and initiation of intravenous gamma-globulin⁵.

In most of the above reported cases, the presence of neurological manifestations after anti-TNF induction, the exacerbation of symptoms during reexposure to the drug, and their improvement after treatment discontinuation suggest an association between anti-TNF therapy and these neurological complications.

Peripheral neuropathy probably represents another complication associated with infliximab treatment. Clinicians should be aware of the above complication, and close neurological monitoring in patients receiving anti-TNF agents seems mandatory.

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Dr. Zochodne replies

To the Editor:

We appreciate the interest in our article and the comments in the above letters. We agree with some of these comments and disagree with others. Drs.

Roos and Ostor raise the issue of PML, undiagnosed JC virus infections, and the pace of neurological investigations in patients with white matter disease. We agree that PML, a condition with which we are very familiar [described pathologically in a report some years ago by one of us (DZ)]¹, has emerged as an important, although very rare complication of natalizumab and can portend a serious prognosis. As pointed out by Roos and Ostor, its mechanism of action is different than that of infliximab. We await rigorous peer-reviewed data on its prevalence in anti-TNF- α therapy.

We disagree with comments on the pace and type of investigation of white matter disease in cases like ours. From the perspective of neurological care, clinical judgment remains paramount in how central nervous system white matter lesions (common neurological problems, sometimes of no clinical significance, and very few with "rapidly fatal" courses) should be investigated for PML and when. More data are likely required as to the role, sensitivity, and specificity of testing for JC virus in wider clinical settings. Pathological diagnosis remains the gold standard for identification of this condition. There is no debate that anti-TNF- α therapy should be withheld in the setting of unexplained new neurological disease. Unfortunately, there is no current evidence that immediate investigation for JC virus, in patients who do not have a clinical course or white matter disease that suggests PML, would be helpful. No direct treatment for the virus has had high quality evidence of efficacy. Finally, PML does not target the peripheral nervous system.

We agree with the comments by Dr. Tektonidou about when to suspect a neurological complication from infliximab and how to respond to it. We recognize that other reports of neuropathy have emerged during submission and handling of our work and believe that claims of precedence have no role in these kinds of reports. We have also had direct experience with a previously reported clinical trial of therapy for multifocal motor neuropathy², but do not feel our cases had this phenotype. Overall, we concur that greater recognition and published reports to identify the range of complications possible with infliximab and related agents are required.

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Interstitial Pneumonitis and Anti-Tumor Necrosis Factor- α Therapy

To the Editor:

Villeneuve, *et al* report a case of interstitial pneumonitis in a patient with rheumatoid arthritis (RA) receiving infliximab therapy¹. This case would add to the growing body of evidence concerning this rare complication of tumor necrosis factor- α (TNF- α) antagonist therapy.

We have some reservations, however, as to whether the disease process they describe marries with the existing published cases of interstitial lung disease (ILD) following biologic therapy. There are now, in fact, more than 20 published cases in the literature where treatment with infliximab, etan-

cept, or adalimumab has led to the rapid evolution of noninfectious ILD, normally occurring after the second or third treatment²⁻⁸. Unlike in the case of Villeneuve, *et al*, the patients reported to date typically had preexisting mild or asymptomatic ILD. The case described by Villeneuve, *et al* also differs from the other published cases in that an infectious organism, aspergillus, was isolated on bronchoalveolar lavage (BAL). TNF- α -modulating drugs are well known to predispose to infection⁹ and, indeed, in Villeneuve's report the patient's respiratory symptoms resolved following treatment with caspofungin and itraconazole.

The diagnosis of interstitial pneumonitis in Villeneuve's case was not confirmed histologically, and we note that BAL did not reveal an increased number of mast cells as may be expected in usual interstitial pneumonia (UIP)¹⁰. We recently described 5 cases of infliximab-induced ILD in *The Journal*; a histological diagnosis was obtained in 4⁷. Of these, the 3 who died had developed UIP. One patient survived and was found to have developed bronchiolitis obliterans organizing pneumonia (BOOP). In the fifth patient, who also died, autopsy was refused but high resolution computed tomography was suggestive of UIP.

Though there are still too few biopsy-diagnosed cases to be certain, we suspect that the type of ILD may greatly affect outcome, with UIP marking the severe end of the spectrum and BOOP perhaps the milder, with better prognosis. If this is true, it is possible that Villeneuve's patient developed a self-limiting BOOP, as was the case in the one patient from our report who also survived.

The conclusion drawn by Villeneuve, *et al* — that infliximab may potentiate the pulmonary toxicity of methotrexate (MTX) — could be correct, but there is currently no evidence for this. Certainly 11 out of 20 patients reported to date were not taking MTX with their anti-TNF- α therapy. The literature suggests instead that TNF- α -modulating drugs are independently capable of precipitating ILD in the absence of MTX^{2,3,7,8,11,12}. These adverse events are not limited to RA and have been reported in patients treated for systemic sclerosis, Crohn's disease, and ankylosing spondylitis^{8,11,12}. Physicians who prescribe biologics should be aware that potentially devastating noninfectious pulmonary complications can occur on biologic monotherapy, that is, in the absence of MTX or any other disease modifying antirheumatic drugs.

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Dr. Villeneuve, et al reply

To the Editor:

We thank Dr. Roos and colleagues for their comments about our case report of infliximab-induced pneumonitis¹. As they mentioned, there are indeed some differences regarding our case and the ones they have reported, but this may highlight the different types of interstitial lung disease (ILD) that can be associated with infliximab therapy.

Ostor, *et al*² have reported 5 cases of infliximab-induced ILD, 4 of them with usual interstitial pneumonia (UIP) confirmed by pathology or high resolution chest tomography. We agree that, unlike those patients, our patient did not develop an accelerated form of UIP. As they have highlighted, our patient had no history of lung disease and no increased number of mast cells on bronchoalveolar lavage (BAL) that could be suggestive of UIP. But those findings are also true for the 6 other cases that have been reported, where infliximab seemed to have precipitated MTX-induced pneumonitis^{3,4}. Indeed, the lymphocytosis found on the BAL and the reversal of symptoms with corticosteroid treatment and the withdrawal of infliximab are more suggestive of a drug-induced acute interstitial pneumonitis than a UIP. Those different presentations could be because infliximab may induce an accelerated form of UIP with poor prognosis in RA patients with preexisting ILD, or induce a more reversible form of drug-induced pneumonitis or of bronchiolitis obliterans organizing pneumonia (BOOP), similar to the fifth case reported by Roos, *et al*.

Our case also differs in that aspergillus was isolated on the BAL. But as we stated, after discussion with the microbiologist and the pulmonologist, it was considered to be a colonizing organism because it was found in only half the samples and the aspergillus antigen detection assay was negative. In fact, the patient did not improve with caspofungin therapy and only started to improve when he was treated with high-dose corticosteroids. Itraconazole was administered as a prophylaxis with the goal of preventing aspergillus reactivation while the patient was immunosuppressed with the high-dose corticosteroids. With the growing number of infliximab-induced ILD, we are able to better appreciate this rare but severe complication of TNF- α antagonist therapy. Infliximab seems to be able to induce different types of ILD ranging from BOOP to an accelerated form of UIP. Patients with preexisting lung disease seem to have a much worse prognosis and they should be informed about the risk of ILD before they receive infliximab therapy. This could also be true for other anti-TNF- α agents, but there is insufficient evidence for this at the moment.

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Adalimumab-Associated Multiple Sclerosis

To the Editor:

Several cases of demyelinating diseases have already been reported during the course of tumor necrosis factor- α (TNF- α) antagonists. We describe a case of multiple sclerosis (MS) where onset was associated with adalimumab.

A 32-year-old woman with rheumatoid arthritis (RA), who had unsuccessfully been taking methotrexate for 16 months, started taking adalimumab in April 2003 (40 mg/2 weeks). In March 2005, she reported an acute loss of vision with pain in her left eye. A retrobulbar optic neuritis was diagnosed. Adalimumab was discontinued and a 3-day course of high-dose methylprednisolone started. Her visual acuteness improved but an afferent papillary defect remained in her left eye. Magnetic resonance imaging (MRI) demonstrated multiple lesions in the white matter with high signal intensities (T2-weighted images) and enhancement after gadolinium (T1-weighted images) in the right and left semi-oval centers. Three months later, the MRI showed new gadolinium enhancing lesions leading to the diagnosis of MS according to the revised McDonald criteria¹.

The temporal relationship between adalimumab and MS and the partial improvement of optic neuritis after its discontinuation raise the question of the role of adalimumab. So far, only 2 cases of optic neuritis had been published with adalimumab, one with isolated optic neuritis and one with numerous central nervous system (CNS) plaques of various ages and a painful retrobulbar optic neuritis². Four additional cases of CNS demyelination have been identified during the adalimumab clinical development program. One patient presented with optic neuritis and the other 3 with paresthesia. One of them had a prior diagnosis of probable MS³.

A link between TNF- α antagonists and a demyelinating disease is suggested by several studies. Based on the TNF- α overproduction in serum and cerebrospinal fluid of patients with MS⁴ and the effect of TNF- α antagonists in animal models⁵, a double-blind, placebo-controlled trial in MS with lenercept (TNF- α antagonist close to etanercept) was conducted. Unfortunately, this led to a shortening of time to flare, and a worsening of the neurological condition⁶. Similar outcomes have also been observed in an open-label trial with a monoclonal anti-TNF antibody in 2 patients with rapidly progressive MS⁷.

These studies suggest that TNF- α antagonists may potentially initiate or unmask an underlying demyelinating disease. New onset, flare, or worsening of demyelinating diseases including MS have been associated with the 2 other marketed TNF- α antagonists (17 with etanercept and 2 with

infliximab)⁸. An update through August 2002 from the US Food and Drug Administration's AERS database has also reported several cases of demyelination associated with infliximab, but detailed information about these cases is not published⁹. In the French adverse event reporting system database, 4 demyelinating disorders (worsening 1, new onset 3) have been reported during treatment with infliximab over 4 years and etanercept over 5 years, respectively. However, all these data must be tempered by cases of demyelinating diseases recently reported in patients with RA who were not receiving any TNF- α antagonists⁹.

Like other TNF- α antagonists, adalimumab must be stopped if a neurological event occurs and should be avoided in patients with preexisting or suspected demyelinating diseases.

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Dr. Toussiot replies

To the Editor:

Bensouda-Grimaldi, *et al* reported an additional case of demyelinating disease occurring in a patient receiving adalimumab for rheumatoid arthritis

(RA). Since the beginning of the use of anti-TNF- α therapy, a limited number of neurological events have been described in patients receiving these agents for RA or other inflammatory conditions. These events included exacerbation of preexisting multiple sclerosis (MS), new onset MS, miscellaneous neurological symptoms (including optic neuritis, dysesthesia, paresthesia, motor deficits, or mental status changes)¹. The relationship between the development of these events and anti-TNF- α therapy is still debated. The 3 available TNF- α antagonists have been associated with these neurological symptoms, most cases with etanercept. This apparent preferential association is unclear: in MS clinical studies, both infliximab, a monoclonal antibody, and lenercept, a soluble p55 TNF receptor fusion protein, have been associated with increased disease activity. TNF- α probably plays a dual role for white matter lesions in MS. Indeed, animal models of MS provided evidence that TNF- α may exacerbate or, conversely, protect the central nervous system during the development of demyelinating disease: TNF- α antagonists prevent and ameliorate experimental allergic encephalomyelitis (EAE) while in TNF- α null mice, they exacerbate EAE.

The most convincing arguments for a neurological side effect induced by anti-TNF- α treatment were the temporal relation and the resolution on discontinuation. Conversely, there are some factors arguing against a direct role for anti-TNF- α : these cases were reported with a low incidence, below the natural incidence of MS in the general population, and they may represent coincidental events. It has also been speculated that these neurological syndromes may be a clinical manifestation of another autoimmune disease occurring in a patient with a propensity to develop MS due to common genetic background, suggesting that anti-TNF- α treatment unmasks the demyelinating disease. Indeed, MS has been associated with various autoimmune diseases, including RA^{2,3}. It should also be interesting to carefully examine whether patients with a disease that is not commonly associated with MS (such as psoriasis, psoriatic arthritis, or Crohn's disease) could develop MS or MS-like disease during anti-TNF- α administration. Curiously, there is no report of demyelinating disease in patients with ankylosing spondylitis receiving anti-TNF- α therapy, and this disease has been associated with MS.

Finally, the neurological potential effects of TNF- α antagonists are not limited to the central nervous system. Indeed, some cases of peripheral neuropathy with varying degrees of motor and sensory involvement were recently reported in RA patients receiving infliximab⁴.

All these data highlight the need for careful clinical evaluation, including neurological examination, before starting anti-TNF- α treatment. Patients with unexplained central nervous system involvement or signs of peripheral neuropathy, with past history or familial history of demyelinating disease, should not receive this treatment before complete neurological evaluation. Finally, reporting of all new cases of demyelinating or neurological disease during the course of anti-TNF- α treatment is required to better understand the potential neurological effects of TNF- α antagonists in RA, but also in all other diseases receiving this effective class of drugs.

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Macrophage Activation Syndrome After Etanercept Treatment

To the Editor:

Macrophage activation syndrome (MAS), a secondary form of a hemophagocytic lymphohistiocytosis syndrome (HS), involves uncontrolled T cell-induced proliferation and activation of macrophages¹. The subsequent cytokine storm and infiltration of tissues by phagocytosing macrophages result in an acute life-threatening disorder². To date, MAS has been linked to various viral infections [Epstein Barr Virus (EBV), cytomegalovirus (CMV), and parvovirus], autoimmune disorders [rheumatoid arthritis (RA), systemic lupus erythematosus], lymphomas, and leukemias³. Case reports of rheumatoid patients with HS, although limited, have suggested an infective or RA precipitant^{4,5}. Some anecdotal reports describe MAS after treatment with anti-tumor necrosis factor- α (TNF- α) agents⁶. We describe a patient with RA who may have developed MAS after taking etanercept.

A 42-year-old woman with a history of RA presented to hospital with a 2 month history of fever, chills, night sweats, rigors, and a dry cough in August 2005. She had no recent travel or transfusion history and denied any history of headaches, respiratory, gastrointestinal, or genitourinary symptoms. Her medications at the time of admission consisted of prednisone (5–10 mg/day), folic acid, and ketoprofen (100 mg po bid). Immunosuppressive therapy with azathioprine had been discontinued 6 months before due to abnormal liver function tests, and etanercept was discontinued 2 months before because of unexplained fevers. Before this, she had been taking azathioprine for 15 years and etanercept for 2 years. During her 2 month period of fevers, management by her family doctor included a normal chest radiograph and a trial of antibiotics for suspect urinary tract infection.

Examination revealed a temperature of 38°C, blood pressure 135/90 mm Hg, heart rate 96 beats/min, respiratory rate 18/min, and oxygen saturation of 99% on room air. Physical examination was significant for hepatosplenomegaly. There were no tender/effused joints, lymphadenopa-

thy, or petechiae present. Her initial laboratory investigations revealed leukopenia (1200/mm³), anemia (hemoglobin 111 g/l), and hepatitis (ALP 218 IU/l, AST 200 IU/l, ALT 57 IU/l, and bilirubin 12 IU/l; Table 1). Routine blood tests, urine, blood, stool, and sputum cultures were negative. A chest radiograph was normal. Viral serology and antigen testing for CMV, parvovirus, EBV, hepatitis B and C were negative. Serum polymerase chain reaction for EBV was negative. Admitting diagnosis was febrile neutropenia and she was given tobramycin and cefazolin. Her fevers lasted only during the initial period of her admission.

She developed progressive liver failure with icterus about 10 days after admission, with increasing international normalized ratio, partial thromboplastin time, and bilirubin levels. Additional laboratory values included C-reactive protein of 243 mg/l, erythrocyte sedimentation rate of 19 mm/h, D-dimers 4690 mg/l, ferritin 56,783 μ g/l, and lactate dehydrogenase 4844 IU/l. A bone marrow examination showed several small poorly formed granulomas, as well as focal macrophages exhibiting hemophagocytic activity in the bone marrow (Figure 1). Stains for acid-fast bacillus and fungi were negative as well as immunohistochemistry for CMV and *in situ* hybridization for EBV. Our patient was diagnosed with MAS and given cyclosporine (5 mg/kg), intravenous immunoglobulin (0.5 mg/kg for 2 days), and dexamethasone (10 mg/m²). Then she developed a gram-negative bacilli septicemia and acute renal failure. She was transferred to the intensive care unit, where all immunosuppressant therapy was discontinued. She developed anasarca and 2 weeks later died of acute respiratory distress syndrome and multiorgan failure considered secondary to sepsis and uncontrolled MAS 6 weeks after admission.

Our patient developed MAS about 2 months after etanercept was discontinued due to her presenting complaint of a fever of unknown origin. The MAS precipitant may have been a preceding infection or pharmacologic agent, such as ketoprofen¹⁰. Patients with MAS typically present with a high grade fever, pancytopenia, hepatosplenomegaly, and lymphadenopathy with liver insufficiency. Patients may then develop purpura and mucosal bleeding. Diagnosis of a HS involves 8 criteria of which 5 must be satisfied⁷. During the course of this case, 6 of these criteria were achieved: the patient experienced a fever of at least 2 weeks, splenomegaly, cytopenia, hypertriglyceridemia (14.66 mmol/l)/ hypofibrinogenemia (0.2 g/l), macrophage infiltrate within the bone marrow with hemophagocytosis, and finally, hyperferritinemia (56,775 mg/l). Soluble CD25 and natural killer cell activity were not assayed.

Evidence derived from studies using pediatric cohorts form the basis of treatment regimens for adult forms of HS⁸. Immunosuppressive therapy consisting of a course of etoposide, dexamethasone, and cyclosporine is supported by the best available evidence⁷. Etoposide was contraindicated because of her liver failure. An absence of randomized trials necessitates the

Table 1. Laboratory values, with associated admission day. Patient was admitted on day 1 and began taking immunosuppressants on day 18. Immunosuppressants were discontinued and patient transferred to intensive care on day 25. She died on day 42.

| Laboratory Findings | Hospital Day | | | | | | | |
|---------------------------------------|--------------|--------|-------|--------|--------|-------|------|------|
| | 1 | 4 | 18 | 20 | 22 | 25 | 26 | 41 |
| Hemoglobin g/l | 111 | 111 | 76 | 60 | 101 | 69 | 89 | 70 |
| White blood cells, 10 ⁹ /l | 1.2 | 0.5 | 1.1 | 3.1 | 6.2 | 2.1 | 1.9 | 1.2 |
| Platelets, 10 ⁹ /l | 138 | 113 | 36 | 56 | 40 | 47 | 33 | 16 |
| Neutrophils, 10 ⁹ /l | 0.5 | | 0.5 | 1.9 | 4.6 | | 1.6 | |
| Creatinine, μ mol/l | 46 | 47 | 42 | | 45 | 107 | 131 | 22 |
| Ferritin, μ g/l | | 22,590 | | 56,755 | 39,273 | | 5484 | |
| Bilirubin, μ mol/l | | 14 | 112 | 82 | 132 | 89 | 157 | 166 |
| International normalized ratio | 1.2 | 1.46 | 1.19 | 1.56 | 1.08 | 1.26 | 1.22 | 0.97 |
| Fibrinogen, g/l | | | 0.8 | 0.5 | 0.7 | 3.1 | 3.2 | |
| Triglycerides, mmol/l | | | 21.71 | | | 14.66 | | |
| ALP, IU/l | 218 | 364 | 1351 | 1620 | 1573 | 176 | 191 | 530 |
| ALT, IU/l | 57 | 63 | 60 | 88 | 66 | 26 | 28 | 135 |
| AST, IU/l | 200 | 313 | 413 | 587 | 345 | 98 | 70 | 184 |

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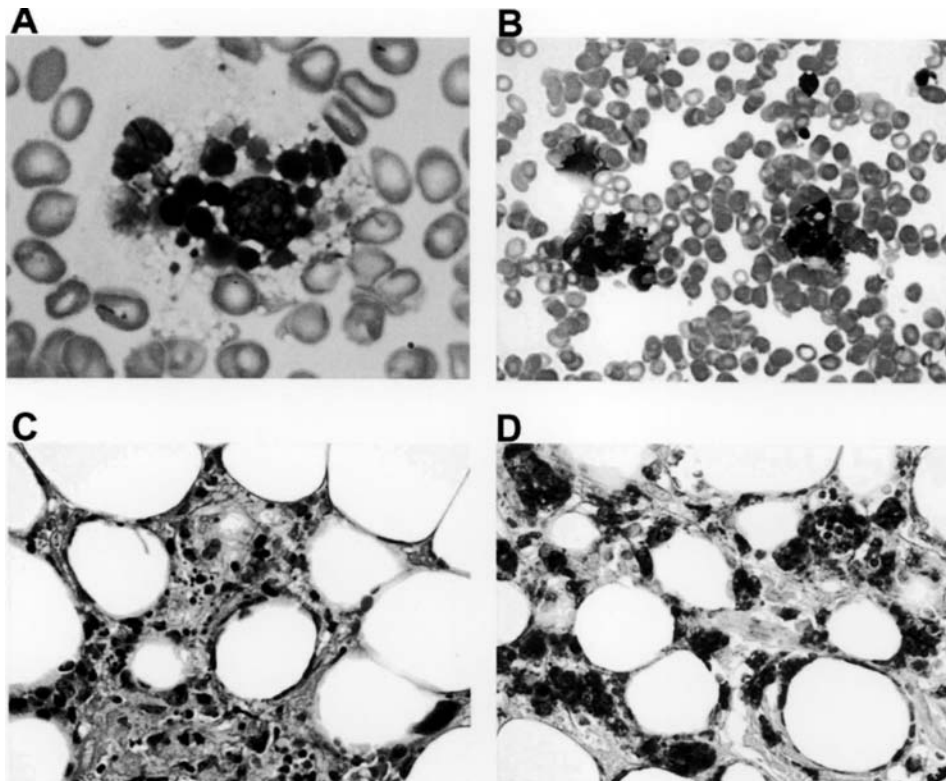


Figure 1. A and B. Hematoxylin and eosin stain of bone marrow aspirate. C. H&E stain of bone marrow core biopsy. D. Bone marrow core biopsy immunohistochemical-stained with anti-CD68 cell surface marker (KP1 clone, Dako).

use of case reports for insight into the management of MAS in adults. Treatment with immunosuppressants may cause a reduction in mortality in adults where HS was precipitated by an underlying autoimmune process. Patients presenting with an active infection required antibiotic therapy and a reduction in immunosuppressive therapy⁴. Other treatment modalities used for the treatment of HS include intravenous IgG, with reports of overall response rates of 59% in patients with HS⁹. However, early diagnosis and initiation of treatment remains critical for effective management of HS³.

While MAS is relatively uncommon, our patient serves to heighten awareness of this condition as a potential complication of both RA and, possibly, anti-TNF- α agents used in treatment.

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