Macrophage Activation Syndrome and Etanercept in Children with Systemic Juvenile Rheumatoid Arthritis

To the Editor:

We read with interest the article by Ramanan, et al describing a patient with systemic onset juvenile rheumatoid arthritis (JRA) who developed a clinical and laboratory picture consistent with macrophage activation syndrome (MAS) following etanercept therapy. We describe a patient with a similar presentation who developed MAS while taking etanercept; however, the cause of disease activation was found to be Epstein-Barr viral (EBV) infection.

A 10.5-year-old Caucasian girl presented in December 1995 with an 8-week history of intermittent fever, characteristic rash, polyarthritis, and morning stiffness and was diagnosed with systemic onset JRA. She was initially treated with prednisone, naprosyn, and methotrexate (MTX) with partial response. In June 1999, she started taking etanercept 0.4 mg/kg subcutaneous biweekly to achieve full clinical remission. She tolerated it well with no complication, and JRA manifestations completely resolved within 6 months of therapy. She remained in remission for the next 2 years while taking MTX and etanercept.

In June 2001, she presented to a local hospital with high grade fever of 106°F. Examination revealed an enlarged spleen and normal liver span, with no lymphadenopathy and no evidence of arthritis. Laboratory evaluation showed low hemoglobin concentration (6.8 g/dl), low platelet count (43,000/µl), low white blood cell count (2300/µl), and high prothrombin time (17.9 s), high international normalized ratio (1.92) and elevated erythrocyte sedimentation rate (31 mm/h). Her liver profile showed elevated liver enzymes including ALT 306 U (normal 24 U), AST 140 U (normal 36 U), and alkaline phosphatase 831 U. A bone marrow biopsy showed erythroaglobocytosis with normal iron stores. Her MTX and etanercept were stopped at the time of admission.

Over the next few days, she continued to have moderate to high grade fever with deterioration of her general condition, and she was transferred to the intensive care unit for further care. She was given antibiotics for possible sepsis, although her blood and urine cultures obtained at the time of admission were negative.

Serological tests for viral infections including hepatitis and cytomegalovirus were negative. On Day 4, the IgM antibody titers against viral capsid antigen became positive, indicating a recent EBV infection. A diagnosis of MAS was made on the basis of pancytopenia, elevated liver enzymes, coagulopathy, persistent fever, and bone marrow findings. She was treated with intravenous methylprednisolone and cyclosporine followed by prednisone. Her clinical and laboratory measures showed marked improvement over the next few days. She was discharged home on a tapering dose of oral prednisone. In a followup visit 2 weeks later she was doing well and the MTX and etanercept were restarted.

This case bears many similarities to the case described by Ramanan and colleagues; however, EBV infection and not etanercept was found to be a possible trigger for MAS in our patient. In the absence of a definitive causal relation between etanercept and MAS, we are reluctant to accept that etanercept alone may induce MAS. Although Ramanan and colleagues ruled out EBV infection, other uncommon viral infections might have been a trigger in their patient.

Few studies have actually found etanercept to be useful in the treatment of MAS. Etanercept continues to be invaluable for therapy of JRA as well as many other rheumatic disorders, and while it is important to encourage continuous surveillance and report side effects, it is also important and prudent to avoid generating undue alarm regarding uncertain and not well proven effects.

HAROON SARWAR, MD, Clinical Rheumatology Fellow, Section of Rheumatology, Department of Medicine; LUIS R. ESPINOZA, MD, Professor of Medicine, Chief, Rheumatology Section, Department of Medicine; ABRAHAM GEDALIA, MD, Professor of Pediatrics, Chief, Division of Pediatric Rheumatology, Department of Pediatrics, LSU Health Sciences Center and Children’s Hospital of New Orleans, 200 Henry Clay Avenue, New Orleans, Louisiana 70118, USA.

REFERENCES

Drs. Ramanan and Schneider reply

To the Editor:

We thank Sarwar, et al for their interest in our article. The patient they describe developed macrophage activation syndrome (MAS) after being maintained on etanercept for 2 years. A similar result has been reported by others as well. Our patient was different in that she developed MAS within 2 weeks (4 doses) of initiation of etanercept, which she had never received before. Our patient also developed giant urticaria at the injection site that heralded the onset of MAS.

We were not able to identify any of the typical viral triggers that have been associated with MAS. The viral serology was negative for Epstein-Barr virus, cytomegalovirus, adenovirus, and parvovirus B19. As we did not do a bone marrow aspirate, testing for viruses by polymerase chain reaction (PCR) in the marrow could not be done.

We did acknowledge in our report that etanercept has been used in the acute management of MAS. However, the same center that published this case report has now described 2 patients who developed MAS while taking etanercept. It is unclear whether MAS occurred when these patients were...
maintained on etanercept or after initiation of therapy, as seen in our patient.

Children with systemic onset JRA seem to be susceptible to developing MAS after initiation of a number of therapies, including second injection of gold, nonsteroidal antiinflammatory drugs, and methotrexate.

We agree with Sarwar and colleagues that etanercept is a valuable agent in the management of JRA. While we concur that it is important not to generate undue alarm about etanercept, we believe that increased vigilance for MAS is required in children who are starting this therapy. Our case report highlights this, and also that giant urticaria at the injection site of etanercept may perhaps herald the onset of MAS.

ATHIMALAPIET V, RAMANAN, MRCP(UK), MRCPCH(UK), RAYFEL SCHNEIDER, MBBS, FRCPC. Division of Rheumatology, Department of Pediatrics, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.

REFERENCES


Therapeutic Implications for Interferon-α in Arthritis

To the Editor:

We read with interest the article by Wong, et al7 on their experiments indicating that interferon-α (IFN-α) might be useful in the treatment of rheumatoid arthritis (RA) through the effects it exerts on cytokines and soluble cytokine receptors by augmenting osteoprotegerin (OPG) gene expression and the production of interleukin 1 receptor antagonist (IL-1Ra) and soluble tumor necrosis factor receptor (sTNFR) in synovial tissue or synovial fluid. IFN-α is a "pleiotropic" cytokine and has been shown to exert immunostimulatory as well as immunosuppressive effects. Reports by Wong, et al and others have described the immunosuppressive and antiinflammatory effects of IFN-α. It decreases the levels of IL-8, whereas

sTNFR-I (p55), sTNFR-II (p75), and IL-1Ra are increased and probably antagonize the action of the respective cytokines, as shown in patients with hepatitis C and in in vitro experiments1,7, and reviewed by Kaser and Tilg7. Matrix metalloproteinase 9 (MMP-9) gene expression (MMP-9 being one of the most important mediators of cartilage destruction) has recently been shown to be decreased by IFN-α, also a type I interferon7.

Our own observations in patients with Behçet’s disease treated with IFN-α, in concordance with the data of Wong, et al, also revealed an increase in sTNFR-II and IL-1Ra in serum (in press). However, Wong, et al do not discuss that IFN-α also induces HLA class I expression, increases the numbers of B cells, and activates monocytes/macrophages8-11. Further, TNF-α gene expression and serum levels (in press) are increased by IFN-α7. Thus it not only improves antigen presentation and elimination of foreign antigens, but may also induce autoimmune phenomena. Autoimmune thyroiditis and SLE have been described to occur as adverse effects of IFN treatment12-14. As for systemic lupus erythematosus (SLE), it has become clear that plasmacytoid dendritic cells, which are the naturally occurring main producers of IFN-α in vivo, play a major role in the pathogenesis of SLE15.

The authors might also have discussed that cases of RA occurred during IFN-α treatment for diseases such as carcinoma, lymphoma, chronic myelogenous leukemia, and hepatitis B and C16,17. Thus, it must be considered that if patients with RA were treated with IFN-α, the proinflammatory actions of this cytokine (mainly the monocyte activation with the resulting increase in TNF-α and B cell activation) might outweigh the antiinflammatory ones (such as the increase in sTNFR-II and IL-1Ra and inhibition of OPG gene expression), resulting in increased disease activity. It might be possible that IFN-α exerts differential effects depending on the immunological background (e.g., Th1, Th2, or Th6).

The results of the preclinical studies announced by the authors will be of great interest.

INA KÖTTER, M.D., Senior Physician, Department of Internal Medicine II, Haematology, Oncology, Immunology and Rheumatology; NICOLE STÜBIGER, M.D., Department of Ophthalmology I, University Hospital, Otfried-Müller-Str. 10, D-72076 Tübingen, Germany.

E-mail: ina.koetter@med.uni-tuebingen.de

REFERENCES


9. Nelissen I, Martens E, Van Den Steen PE, Proost P, Ronnes I,
Dr. Fish replies

To the Editor:

Drs. Kötter and Stübiger are correct in their discussion of the heterogeneity of response to interferon (IFN). The development of autoimmune phenomena during IFN treatment of patients for hematological diseases and hepatitis C virus (HCV), albeit at a low incidence, is a concern that was duly noted in our report. Interpatient variability within a specific disease population certainly confounds the explanation for susceptibility for these adverse events.

The chronic inflammation in rheumatoid arthritis (RA) that leads to joint destruction is characterized by the accumulation of leukocytes within synovial tissues. In RA, the character of the inflammatory infiltrate that defines the disordered synovial environment fluctuates during the course of disease in affected joints, with regard to cell makeup and activation state. Thus cellular interactions that determine cytokine production are also in a constant state of flux. It is the very nature of IFN-γ as pleiotropic biological response modifiers that suggests their therapeutic potential: their ability to target different cell populations, thereby affecting cellular communication and immunological control at multiple levels.

The challenge, as indicated by Drs. Kötter and Stübiger, is to develop a treatment protocol for IFN intervention that will specifically and preferentially promote the antiinflammatory events we reported. Certainly, Kötter, et al recently reported that IFN-α may be superior to the standard immunosuppression treatments for oculocutaneous Behçet’s disease, yet they identified incidents of autoimmune phenomena in 16% of their patient population. Undoubtedly, the nature of the underlying disease, whether it is a hematological malignancy, a chronic viral infection or an autoimmune disease, the specific target tissues, and the immune-genetic background define the spectrum of potential IFN-inducible outcomes. Thus, IFN-α treatment may predictably invoke autoimmune phenomena in selected patients with HCV that might not develop in patients with RA. As with Behçet’s disease, the potential beneficial effects of IFN therapy in a majority of patients with RA may outweigh adverse or exacerbated disease in another specific subset. The intent would be to predetermine responsiveness in each patient, by defining inclusion and exclusion criteria for IFN treatment, based on established leukocyte and fibroblast responses ex vivo. These criteria are under consideration, initially in preclinical studies.

ELEANOR N. FISH, PhD, Director, Arthritis and Autoimmunity Research Centre, University Health Network, 67 College Street, Room 4-424, Toronto, Ontario M5G 2M1, Canada. E-mail: en.fish@utoronto.ca

REFERENCE


False Positive Parvovirus Serology

To the Editor:

In July 1999 we submitted for publication a case report that described the association of an acute symmetrical polyarthropathy with cranial mononeuropathies. Parvovirus B19 IgM was present in the serum and no other cause for the arthropathy or neuropathy was found. Our report was provisionally accepted, but at the suggestion of a reviewer, the parvovirus B19 IgM and IgG titers were repeated 14 months after the original assay, as well as polymerase chain reaction (PCR) analysis for parvovirus B19 DNA, at the Central Public Health Laboratory (CPHL) in London, UK. The results are given in Table 1.

In view of these findings, a further opinion was sought from Prof. Klaus Hedman at the University of Helsinki, Finland, whose assay results are illustrated in Table 2.

These results are consistent with post parvovirus B19 infection, and the anomalous parvovirus B19 IgM results are probably false-positive due to nonspecific reactions, and are not related to recent infection (personal communications, Dr. B.J. Cohen, CPHL, London, UK, and Prof. K. Hedman, University of Helsinki, Helsinki, Finland). On reviewing the initial serum sample results showing persistent parvoviral IgM titer, we withdrew our report. We now wish to draw attention to this case as an example of the doubtful specificity of parvovirus B19 IgM serology that may be encountered by investigators. We would recommend that, where a positive parvoviral IgM is detected, B19 DNA PCR may be necessary to confirm recent infection, where this is clinically necessary.

Table 1. Parvovirus B19 results at CPHL.

<table>
<thead>
<tr>
<th>Date of Serum Sample</th>
<th>B19 IgM in-house EIA’ (T/CO)</th>
<th>B19 IgG Biotrin EIA (T/CO)</th>
<th>B19 DNA PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 25, 1998</td>
<td>3.0 (positive)</td>
<td>8.5 (positive)</td>
<td>Negative</td>
</tr>
<tr>
<td>November 10, 1999</td>
<td>5.2 (positive)</td>
<td>8.3 (positive)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

EIA: enzyme immunoassay, PCR: polymerase chain reaction. CPHL: Central Public Health Laboratory.

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Table 2. Parvovirus B19 IgG avidity and epitope type-specific antibody results.

<table>
<thead>
<tr>
<th>Date of Serum Sample</th>
<th>B19 IgG avidity</th>
<th>Second-generation ETS-EIA</th>
<th>B19-DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 25, 1998</td>
<td>34%</td>
<td>475</td>
<td>Negative</td>
</tr>
<tr>
<td>November 10, 1999</td>
<td>42%</td>
<td>120</td>
<td>Negative</td>
</tr>
</tbody>
</table>

B19 IgG avidity
Acute < 15%
Past > 25%

Second-generation ETS-EIA
Acute < 10
Past > 10

B19-DNA
Negative

ETS-EIA: epitope type-specific enzyme immunoassay.

ALICE H. JOHNSON, MRCP; ANDREW GOUGH, MD, MRCP, Department of Rheumatology, Harrogate District Hospital, Lancaster Park Road, Harrogate HG2 7SX, United Kingdom.
E-mail: andrew.gough@hhc-tr.northy.nhs.uk

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