

PostScript

MATTERS ARISING

Soluble TNF receptor treatment does not affect raised TGF β levels in RA

We read with interest the report by Drynda *et al* demonstrating that treatment of rheumatoid arthritis (RA) with anti-tumour necrosis factor α (anti-TNF α) induces subtle changes in the cytokine network such as down regulation of the proinflammatory cytokine interleukin 6 (IL6), but does not affect the persistently high plasma levels of transforming growth factor β (TGF β).¹ Furthermore, they suggest that the latter finding indicates the existence of as yet unknown mechanisms for TGF β overexpression in RA that may predispose a patient to severe infections and altered tumour defence.

Complementary to the observations noted above are our findings using DNA microarray in patients with RA treated with TNF antagonists as compared with patients with RA treated with methotrexate and healthy controls.² A total of 12 000 genes were analysed (human genome U 95 A Array-Affimetrix) and a variety of gene functions, including apoptosis, transcription factors, cell survival, antigen presentation, cartilage degradation, B and T cell function, intracellular signals, transcription genes, adhesion molecules, inflammatory mediators, clotting factors, HLA class II molecules, oncogenes, cytokine production, and cytokine receptor expression, were altered (up or down regulated) in the group receiving TNF antagonists. Of interest, several proinflammatory cytokine receptors including interferon γ , TNF, IL10, and TGF β were found to be down regulated. Therefore, pathway signalling of these cytokines including TGF β may be impaired if their receptors are down regulated.

Altered expression of these genes' function, alone or in combination, may have an impact on the predisposition to infection and tumour defence. Such is the case for the induced TNF α inhibitor down regulation in the expression of C9, B and T cell functions, signalling cascade (\downarrow Jun B), adhesion molecules, heat shock proteins, and antigen presentation, and the predisposition to infection. Likewise, TNF antagonists also regulate the

expression of oncogenes, such as Jun B, c-myc, fos and ras, which may have an impact on tumour defence.

Therefore, our study with DNA microarray confirms and expands the immunomodulatory functions of TNF antagonists. Data, however, seem to suggest that the increased predisposition to develop infection and altered tumour defence may not be related to increased plasma levels of TGF β because its receptors are down regulated, but rather to dysregulation of gene expression of other molecules induced by the TNF antagonists.^{2,3}

R Cuchacovich, L R Espinoza

Section of Rheumatology, Department of Medicine, LSU Health Sciences Center, 1542 Tulane Avenue, New Orleans, LA 70112-2822, USA

Correspondence to: Professor L R Espinoza; jbasco@lsu.mc.edu

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Authors' reply

We read with interest the letter by Cuchacovich and Espinoza commenting on our previous paper,¹ which, based on results of DNA microarrays showing that increased plasma levels of transforming growth factor β (TGF β) persist in the course of anti-tumour necrosis factor α (anti-TNF α) treatment in rheumatoid arthritis (RA), suggests that patients may not have an altered tumour defence.

Complex effects of TGF β on tumour development and progression, as well as cancer metastasis have been demonstrated in numerous studies.^{2,3} As a result of these studies, raised levels of TGF β seen in patients with RA are thought to contribute to an altered tumour defence.

In our own additional experiments we monitored changes in the expression profiles of mononuclear cells from peripheral blood in the course of anti-TNF treatment in RA in 10 patients using the same human genome U95a Affymetrix chip. By applying a different experimental setting than Cuchacovich *et al*,⁴ different results were found. Only a small number of genes were found to be regulated in five or more of the 10 patients in either direction after anti-TNF treatment compared with baseline. Among these genes were proinflammatory cytokines, chemokines, apoptosis related proteins, and proteins involved in the cell cycle. Interestingly, different regulation patterns were found in our patients.⁵ In contrast to Cuchacovich *et al*,⁴ no down regulation was found in receptors for interferon γ , interleukin 10, or in either

TGF β receptors (TGF β RI and TGF β RII) within the first six days of anti-TNF treatment. Expression of oncogenes Jun B, c-myc, ras, and fos remained unchanged as well.

Finally, it should be mentioned that neither mRNA levels nor plasma concentrations of TGF β completely reflect the real situation in vivo because the biological activity of TGF β is tightly regulated post-transcriptionally. This includes the proteolytic cleavage of active TGF β from its precursor protein,⁶ the formation of the active ligand-receptor complex, and the downstream signalling via Smads.⁷

Further research is mandatory to explain the multiple effects of TGF β and its role in the complex network of cytokines. Recently developed techniques such as DNA microarrays may help to understand the interactions and regulation of proteins and their biological activity.

S Drynda, J Kekow

Clinic of Rheumatology, University of Magdeburg, Germany

D Koczan, H-J Thiesen

Institute of Immunology, University Rostock, Germany

Correspondence to: Professor J Kekow, Clinic of Rheumatology, University of Magdeburg, D-39245 Vogelsang/Magdeburg, Germany; Joern.kekow@medizin.uni-magdeburg.de

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Usefulness of bone densitometry in postmenopausal women with clinically diagnosed vertebral fractures

We read with interest the article by Nolla *et al*, which demonstrates that only 3% of patients with symptomatic non-traumatic vertebral fracture have normal bone mineral density (BMD).¹ We agree with their conclusions that in this clinical setting measurement of BMD is not required to confirm a diagnosis of osteoporosis before starting treatment.

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A large number of studies have shown that a previous history of vertebral fracture increases the risk of future vertebral and non-vertebral fracture, independently of BMD.² Vertebral fractures are also associated with significant morbidity, leading to an impaired quality of life³ and increased mortality.⁴ A recent study by Lindsay *et al* demonstrated the speed of disease progression in osteoporosis, with 20% of patients experiencing a new incident vertebral fracture within 12 months after a vertebral fracture.⁵ These data suggest that osteoporosis treatment should be started as soon as possible after a fracture has been diagnosed, as any delay in initiating treatment while waiting for bone densitometry may put the patient at risk of further fractures. The availability of dual energy absorptiometry (DXA) is poor in the United Kingdom in comparison with some other European countries. The Advisory Group Report on Osteoporosis noted that in the UK there were 1.6 DXA machines per million population, compared with 2.9 in the USA and 6.6 in France.⁶ The limitation of DXA machine provision in the UK compared with the clinical demand has led to long waiting lists for BMD measurements and a potential delay in starting osteoporosis treatment.

Under these circumstances, what is the evidence that patients can be treated solely on the basis of vertebral fracture without the need for BMD measurement? The majority of studies have evaluated drug treatment in patients with low BMD alone, or with low BMD and prevalent vertebral fractures. Studies of risedronate,⁷ raloxifene,⁸ and parathyroid hormone⁹ have, however, included patients with two or more asymptomatic vertebral fractures in the absence of BMD readings.

In the study by Harris *et al* 80% of patients had two or more vertebral fractures, and analysis of this subgroup showed that patients treated with risedronate had a 43% reduction in new vertebral fractures at three years compared with those receiving placebo.⁷ A further study of risedronate recruited patients solely on the basis of vertebral fracture history (≥ 2) irrespective of BMD and demonstrated that active treatment reduced the risk of new vertebral fractures by 49% and of new non-vertebral fractures by 33% over three years compared with placebo.⁸

Studies of raloxifene⁹ and parathyroid hormone¹⁰ have also included patients with a vertebral fracture history alone. Although the results of these studies showed an overall reduction in fracture risk, subgroup analysis of the patients with two or more vertebral fractures and no BMD measurement was not performed. It is therefore not possible to determine accurately the effect of treatment in this group.

We feel that the evidence suggests that patients presenting with two or more non-traumatic vertebral fractures should be considered for treatment of osteoporosis without the need for measurement of BMD, after a metabolic or secondary cause of fracture has been excluded. This is reflected in some of the recent guidelines for the management of osteoporosis.

K Moss, R Keen

Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex HA7 4LP, UK

R Keen

Bone and Mineral Centre, Department of Medicine, University College London, London WC1E 6JJ, UK

Correspondence to: Dr K Moss; kayteemoss@hotmail.com

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Author's reply

We thank Dr Moss and Dr Keen for their interest in our article and for their comments, especially relevant for clinical practice. We agree that whenever the availability of DXA is limited, treatment for osteoporosis in postmenopausal women presenting with non-traumatic vertebral fractures can be started without the measurement of BMD.

J M Nolla

Department of Rheumatology, Ciutat Sanitària i Universitària de Bellvitge, Barcelona, Spain

Correspondence to: Dr J M Nolla; 28634api@comb.es

Infection and SLE

We read with great interest the leader by Gilliland and Tsokos on the prophylactic use of antibiotics and immunisation in systemic lupus erythematosus (SLE).¹ We strongly agree that prophylactic treatment against tuberculosis should be considered in certain groups of patients with SLE, and in particular that co-trimoxazole prophylaxis should be used in patients receiving potent cytotoxic treatment such as cyclophosphamide.

However, the important relationship between hypocomplementaemia, splenic dysfunction, and infection in SLE should also be emphasised. In Western countries, pyogenic infection in SLE is a major cause of morbidity

and mortality.² Infection with *Streptococcus pneumoniae* and *Neisseria meningitidis* appears to be particularly important.^{3–5} We have recently seen in our unit six patients with SLE who died in the past five years. Of these, five had overwhelming infection with *S pneumoniae*.

Defective clearance of bacteria by the spleen as a result of functional hyposplenism is likely to be the cause of the increased risk of infection with *S pneumoniae* and *N meningitidis* in SLE. Corticosteroids and other immunosuppressive drugs are also likely to play a part. The spleen is important in the clearance of particulate immune complexes, such as bacteria opsonised with antibody and complement component C3. Its unique microvascular anatomy and perisinusoidal macrophages bearing Fc and complement receptors are essential in this process. Defective splenic clearance of particulate immune complexes has previously been seen in SLE.⁶ Furthermore, patients with SLE often have chronic hypocomplementaemia, even when their disease is inactive, with low levels of C3 and C4 resulting in defective opsonisation of immune complexes. This, together with an acquired reduction in levels of complement receptor type 1 on the surface of erythrocytes, impairs delivery of immune complexes to the spleen.

Also important to mention, although only representing a small group of patients with SLE, are those with homozygous deficiencies of early components of the classical complement pathway. Not only do these deficiencies predispose to the development of SLE but they also increase the risk of infection. For example, among 41 patients with C1q deficiency, 13 had recurrent bacterial infections, including meningitis and pneumonia.⁷ Complement is known to have a vital role in host defence against infection, and may also be important in the processing of Gram negative organisms.⁸ Gram negative infection is also an important cause of death in certain cohorts of patients with SLE.⁹

An increased risk of infection with *S pneumoniae*, *N meningitidis*, and *Haemophilus influenzae* type B is also seen after surgical splenectomy. Such patients should receive lifelong prophylaxis with penicillin V and immunisation with pneumococcal polysaccharide vaccine. Children and adults with asplenia or severe splenic dysfunction due, for example, to coeliac disease, should also receive a single dose of *H influenzae* type B vaccine. We have previously recommended that patients with SLE and chronic hypocomplementaemia should also receive similar prophylaxis¹⁰ and wish to reiterate the importance of these measures in order to prevent life threatening infection in this disease.

A L Hepburn, K A Davies

Rheumatology Section, Division of Medicine, Imperial College School of Science, Technology and Medicine, Hammersmith Hospital, London W12 0NN, UK

Correspondence to: Dr A L Hepburn; a.hepburn@ic.ac.uk

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Authors' reply

We appreciate the opportunity to respond to comments generated by our leader entitled "Prophylactic use of antibiotics and immunisations in patients with systemic lupus erythematosus". Hepburn and Davies address several important issues about the prophylactic use of antibiotics in treating patients with systemic lupus erythematosus (SLE) who also have hypocomplementaemia or functional asplenia, or both. They suggest that the increased incidence of infections with encapsulated organisms in patients with SLE is related to defective clearance secondary to functional hyposplenism, immunosuppressive treatment, and defective opsonisation. All these potential explanations seem plausible, but it is important to note that not all patients with SLE and neisserial infections are receiving immunosuppressive agents at the time of their infection.¹

As emphasised in our article, we agree that it is important to recognise cohorts of patients who are at risk of developing certain infections.² However, in the case of neisserial infections, the evidence to support prophylactic antibiotics for patients with SLE and hypocomplementaemia is not clear. In a small case series of patients with SLE and neisserial infections, Mitchell and colleagues suggested the following possible risk factors: female sex, young age, renal disease, and persistent hypocomplementaemia.¹ Although it is clear that in children with haemoglobinopathies and splenic dysfunction who receive oral penicillin prophylaxis, pneumococcal bacteraemia is reduced dramatically,³ little information supports the use of this strategy in asplenic adults.⁴

In summary, optimal strategies to decrease the incidence of infections should remain a priority for all doctors caring for patients with

SLE. However, in those who are asplenic, we reiterate the importance of vaccinations against pneumococcus and *Haemophilus influenzae* type B. Currently, no data support the role of prophylactic penicillin or other antibiotics in patients with SLE who are asplenic or have persistent hypocomplementaemia, but this should be further investigated with more definitive studies. For now, the best approach for doctors caring for patients with SLE is to immunise them with appropriate vaccinations, consider antibiotic prophylaxis in certain situations, and maintain a high degree of awareness for the diagnosis of bacteria and other pathogens, especially those that are prevalent in the community in which you care for the patients.

W R Gilliland, G C Tsokos
USUHS/WRAIR, 503 Robert Grant Road, Bldg 503, Rm 1A32, Silver Spring, MD 20910-7500, USA

Correspondence to: Dr G C Tsokos;
gtsokos@usuhs.mil

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Was it a case of Takayasu arteritis?

Recently, the case of a 9 year old boy presenting with cardiac failure was presented in the *Annals of the Rheumatic Diseases*.¹ It was reported as a case of Takayasu's arteritis in a child with a CD4+ lymphopenia and dysgammaglobulinaemia. I have a number of problems with this case:

- As presented in table 1 in the letter, this 9 year old child has a normal CD4 cell count with a low total lymphocyte count. Is the table wrong or did this child actually have a normal CD4 lymphocyte count?
- The dysgammaglobulinaemia actually consisted of a modest rise in the IgG level, with a normal IgA, and a borderline low IgM level of rather questionable relevance in such a sick young child.
- The evidence for Takayasu's arteritis is rather circumstantial, based entirely on magnetic resonance imaging with some suggestive clinical findings in a very sick child presenting with cardiac failure. Surely in such a case, especially when the end result was death soon after initiating

immunosuppressive treatment, attempts should have been made to secure a pathological diagnosis, either before or after the final outcome. No mention of this was made in the report.

I remain unconvinced that this was a case of Takayasu's arteritis and there is no evidence presented to suggest that this child did have a CD4+ lymphopenia,

M D Smith

Flinders University of South Australia

Correspondence to: Dr M D Smith, Rheumatology Research Unit, Repatriation General Hospital, Daws Road, Daw Park, South Australia 5041, Australia; Malcolm.Smith@rgh.sa.gov.au

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Author's reply

We thank Dr Smith for his comments and would like to reply to the points he made.

Firstly, we agree that the absolute CD4 number was not correct in the table. It was incorrectly converted in the editorial process from the value/mm³ and should have been 0.2×10⁹/l rather than 2×10⁹/l. We regret that this point was overlooked on the proofs.

Secondly, a polyclonal hypergammaglobulinaemia is present in one third of cases with Takayasu arteritis. The serum immunoglobulin levels of our patient are consistent with Takayasu arteritis. Dr Smith mentioned a modest rise in the IgG level, with a normal IgA level, but our patient had high levels of both IgG and IgA.

Finally, the classification criteria for Takayasu arteritis according to the American College of Rheumatology (ACR) are: (a) age at disease onset in years <40; (b) claudication of the arms and legs; (c) decreased brachial artery pulse; (d) blood pressure difference >10 mm Hg; (e) bruit over subclavian arteries or aorta; (f) arteriogram abnormality. Our patients had all six of these criteria. In addition to the ACR criteria, our patient had one obligatory, one major, and five minor criteria for the clinical diagnosis of Takayasu's disease according to Ishikawa's criteria.¹ These criteria comprise one obligatory criterion, two major criteria, and nine minor criteria. In addition to the obligatory criterion, one major and two or more minor criteria suggest a high probability of the presence of Takayasu's disease.

These data prove that there is no reason to doubt the diagnosis of this case as Takayasu arteritis. Additionally, the patient had a low CD4 count associated with hypergammaglobulinaemia.

S S Kiliç

Department of Paediatrics, Immunology Division, Uludag University Medical Faculty, Görükle- Bursa 16059, Turkey

Correspondence to: Dr S S Kiliç;
sebnemk@uludag.edu.tr

Reference

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