PostScript

LETTERS TO THE EDITOR

If you have a burning desire to respond to a paper published in *Thorax*, why not make use of our ''rapid response'' option?

Log on to our website (www.thoraxjnl.com), find the paper that interests you, and send your response via email by clicking on the ''eLetters'' option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on ''read eletters'' on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

Etanercept in chronic severe asthma

We read with interest the recent open labeled investigation with etanercept as add-on therapy in 15 patients with chronic severe asthma by Howarth and colleagues.[1] In these patients treatment with etanercept (25 mg administered subcutaneously twice a week for a period of 12 weeks) was associated with a substantial improvement in asthma symptoms, lung function, and bronchial hyperresponsiveness (BHR). The clinical improvement was measured by means of the Juniper asthma control questionnaire (ACQ) score; during treatment with etanercept the ACQ score fell considerably from a mean (range) of 26 (9–32) to 11 (4–27).

The most common adverse effects during treatment were respiratory tract infections (58.8%) and asthma exacerbations (52.9%). Ten of the 15 patients presented with respiratory tract infections associated with worsening of asthma control. The majority of asthma exacerbations are caused by acute respiratory viral infections, of which rhinoviruses are by far the most frequent,[2 3] but other respiratory pathogens are also important.[4 5] Immunosuppression induced by the inhibition of TNFα is likely to be the cause of the observed high incidence of respiratory infections in these patients; in man, anti-TNFα treatments have been implicated in increased susceptibility to pneumococcal infection.[6]

Symptoms due to asthma exacerbations in patients with respiratory infections are likely to severely compromise the quality of life of patients with severe chronic asthma. It was therefore surprising to see that the improvement in the ACQ score after etanercept occurred despite the reported high frequency in respiratory tract infections and asthma exacerbations. Perhaps the substantial improvement in asthma symptoms observed in these patients was merely due to increasing the dose of rescue medications used to manage worsening in asthma control. This may explain why etanercept failed to attenuate pulmonary eosinophilia and to reduce BHR to methacholine in a recent randomised, double blind, placebo controlled trial of patients with a mild form of the disease in whom asthmatic exacerbations were never reported.[7] It is therefore important to take into account the overall increase in rescue medications used to control asthma exacerbations as a secondary measure along with the ACQ score.

C Oliveri, R Polosa
Dipartimento di Medicina Interna e Specialistica, Università di Catania, Presidio Ospedaliero Ascoli-Tomaselli, Via Passo Gravina 187, 95125 Catania, Italy; polosa@unict.it

References

1 **Howarth PH**, Babu KS, Arshad HS, *et al*. Tumour necrosis factor (TNFα) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;**60**:1012–8.
2 **Johnston SL**, Pattemore PK, Sanderson G, *et al*. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;**310**:1225–9.
3 **Nicholson KG**, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ* 1993;**307**:982–6.
4 **Allegra L**, Blasi F, Centanni S, *et al*. Acute exacerbations of asthma in adults: role of Chlamydia pneumoniae infection. *Eur Respir J* 1994;**7**:2165–8.
5 **Lieberman D**, Lieberman D, Printz S, *et al*. Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. *Am J Respir Crit Care Med* 2003;**167**:406–10.
6 **Kirby AC**, Raynes JG, Kaye PM. The role played by tumor necrosis factor during localized and systemic infection with Streptococcus pneumoniae. *J Infect Dis* 2005;**191**:1538–47.
7 **Rouhani FN**, Meitin CA, Kaler M, *et al*. Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation. *Respir Med* 2005;**99**:1175–82.

Authors' reply

We thank Drs Oliveri and Polosa for expressing interest in our paper. As they point out, in our open study, respiratory tract infections were common even during the active treatment with etanercept, but since our study was not placebo controlled, it is not possible to say whether or not the frequency or severity of these events were worse or better in response to treatment.[1] While there is good evidence that anti-TNF strategies increase the risk of infection in other chronic diseases such as rheumatoid arthritis,[2] in most studies the soluble receptor fusion protein etanercept results in fewer events than blocking monoclonal antibodies.[3] Moreover, these infections appear to be restricted to opportunistic bacteria or fungi where TNF presumably plays a role in innate defence.[4] A recently reported small crossover placebo controlled study of etanercept in patients with refractory asthma by Berry *et al*[5] revealed a similar number and severity of virus infections in both active and placebo arms. However, they did record the identification of *Haemophilus influenzae* in the sputum from a single patient during the active phase of the trial, but were unable to comment on its significance.

We believe it is unlikely that the marked beneficial effect of etanercept on the asthma control questionnaire (ACQ) and on both symptoms and asthma related quality of life in our study and that of Berry *et al*[5] was due to increasing the dose of rescue medication because, in this steroid refractory group, a 2.5 and 3.5 doubling dilutions reduction in methacholine BHR occurred, as well as improvements in baseline lung function. In addition, in our study all the patients who were taking regular nebulised salbutamol were able to stop this medication. In the study of etanercept on allergen mediated inflammation in mild asthma by Rouhani *et al*,[6] the negative response of treatment might relate to the fact that only four doses of etanercept were given over 2 weeks, which may be insufficient to reveal efficacy since, in our study[1] and that of Berry *et al*,[5] at least 4 weeks of treatment was required before efficacy was apparent.

What is now needed are large randomised controlled trials in which careful account is taken of side effects, which must include infections as well as careful recording of rescue medication as suggested by Drs Oliveri and Polosa. Readers should also be aware of the recently published British Thoracic Society (BTS) recommendations for assessing risk and managing tuberculosis in patients due to start anti-TNF therapy.[7] Based on current knowledge, TNF appears to contribute actively to the pathophysiology of virus induced lung disease[8–10] and, therefore, paradoxically, anti-TNF therapy may prove to be beneficial rather than damaging.[7–9]

S T Holgate, P H Haworth, K S Babu, H S Arshad
Infection, Inflammation and Repair Division, Southampton General Hospital, Southampton SO16 6YD, UK; sth@soton.ac.uk

References

1 **Howarth PH**, Babu KS, Arshad HS, *et al*. Tumour necrosis factor (TNF alpha) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;**60**:1012–8.
2 **Bresnihan B**, Cunnane G. Infection complications associated with the use of biological agents. *Rheum Dis Clin North Am* 2003;**29**:185–202.
3 **Dinarello CA**. Differences between anti-tumor necrosis factor-alpha monoclonal antibodies and soluble TNF receptors in host defense impairment. *J Rheumatol suppl* 2005;**74**:40–7.
4 **Giles JR**, Bathon JM. Serious infections associated with anti-cytokine therapies in the rheumatic diseases. *J Intensive Care Med* 2004;**19**:320–34.
5 **Berry MA**, Hargadon B, Shelley M, *et al*. Evidence of a role for TNF alpha in refractory asthma. *N Engl J Med* 2006;**354**:697–708.
6 **Rouhani FN**, MEiten CA, Kaler M, et al. Effect of tumour necrosis factor antagonism on allergen-mediated asthmatic airway inflammation. *Respir Med* 2005;**99**:1175–82.
7 **British Thoracic Society Standards of Care Committee**. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNFα treatment. *Thorax* 2005;**60**:800–5.
8 **Rutigliano JA**, Graham BS. Prolonged production of TNF-alpha exacerbates illness during respiratory syncytial virus infection. *J Immunol* 2004;**173**:3408–17.
9 **Tobinick E**. TNF-alpha inhibition for potential therapeutic modulation of SARS corona virus infection. *Curr Med Res Opin* 2004;**20**:39–40.
10 **Hussell T**, Pennycook A, Openhsaw PJ. Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology. *Eur J Immunol* 2001;**31**:2566–73.