information in the presence of high-titre RF [2]. However, serological testing for RF is not diagnostic, being predictive of more severe disease in those with known RA. In secondary care, where the pre-test probability of a diagnosis of inflammatory arthritis in patients is high, one may argue that there is a need for CCP antibody testing only for those in whom the diagnosis of RA is not yet clear. However, in primary care, where currently patients are tested inappropriately for RF with a lower pre-test probability, there are many false positives, leading to inappropriately referrals to specialist clinics. The use of anti-CCP antibody testing in this setting may reduce false positive results, inappropriate referral and ultimately prove cost-saving to the health economy.

We undertook a prospective study to examine a new serological approach for the diagnosis of RA in primary care. We hypothesized that a rheumatoid latex test could be used as an initial screening tool, given its relatively high sensitivity and low specificity. Samples from primary care were screened by RF latex testing, and if positive, tested for anti-CCP antibodies. We compared this strategy with the conventional RF latex plus particle agglutination assay (RAPA) currently used for diagnosis of RA in primary care.

We collected 112 new referrals to the rheumatology outpatient department with joint pain who had previously been subjected to RF testing in primary care. Serum samples were tested for RF using a latex test (RF latex at a screening dilution of 1:120), particle agglutination assay (RAPA-positive if titre >1:80) and anti-CCP antibody (Diasorin, Reading, UK). Clinical diagnoses were recorded blindly by an experienced rheumatologist.

Out of 112 patients referred, 31 (27.6%) had a diagnosis of inflammatory arthritis, of whom 13 were diagnosed with definite RA. Fifteen patients were RF latex/RAPA positive of whom nine (60%) had inflammatory arthritis and eight (53%) definite RA. In contrast, nine patients were RF latex and anti-CCP positive, all of whom had inflammatory arthritis and eight out of nine (89%) had definite RA. One patient with an undifferentiated inflammatory arthritis had a negative RF latex and was positive for anti-CCP antibody. Ninety patients were negative for RF and anti-CCP, of whom five were diagnosed with RA (5.6%). Furthermore, of the 80 patients with non-inflammatory joint pain, 5 (6.25%) were latex/RAPA positive and 12 (15%) were latex-positive/CCP-negative, and referred to out patients on this basis; no patient was CCP antibody positive in this group.

This pilot study suggests that using RF latex as a screening test together with anti-CCP antibody (if the latex test is positive) is an effective strategy for screening for RA in primary care. The combination of RF latex testing and CCP antibody testing provides a highly specific screening test for RA, with comparable sensitivity to latex/RAPA. This approach will not pick up those RA patients who are latex negative and CCP antibody positive, although only one such patient was identified in this study. However, such patients would not be picked up anyway with the conventional approach to screening (latex/ RAPA).

Whilst there is a cost implication to this screening strategy, we calculate that within a catchment population of around 400 000 people, we need to reduce inapposite outpatient referrals by only 20 patients/yr to make this strategy cost-effective for the health economy, based on current outpatient tariffs. We believe this approach to serological testing for RA in primary care merits further study [3].

Disclosure statement: The authors have declared no conflicts of interest.

A. Steuer1, J. Watkins1, F. Smith2, L. Day2, F. Demetriadi1, H. Chapel2

1 Department of Rheumatology and 2 Department of Immunology, Wexham Park Hospital, Slough, Berks SL2 4HL, UK

Accepted 7 December 2007

Correspondence to: A. Steuer, Department of Rheumatology, Wexham Park Hospital, Slough, Berks SL2 4HL, UK.
E-mail: alan.steuer@wph-tr.nhs.uk

Three significant cases of neutropenia with etanercept

Sir, Current BSR guidelines do not recommend regular blood count monitoring for anti-TNF therapy [1] as studies have suggested no increase in adverse haematological events [2-4]. We have noted a minority (14.3%) of our patients becoming neutropenic (<2.0×10⁹/l) on anti-TNF [5], predominantly asymptotically [6]. However, not all episodes have been without concern. Here we describe three cases of significant neutropenia on etanercept.

A 57-yr-old lady with aggressive seropositive RA since 1984 was intolerant of multiple DMARDs. She was on methotrexate and prednisolone (<10mg), but with persistent synovitis. An isolated episode of asymptomatic neutropenia of 1.26 during methotrexate therapy was documented. She started etanercept 25mg twice weekly, with excellent response. She became neutropenic 7 weeks after first dose (1.76×10⁹/l) and persisted throughout treatment, the lowest being 0.84×10⁹/l. These episodes responded to increased prednisolone up to 5mg. Bone marrow examination showed active haemoipoiesis and white cell production with increased immature granulocyte production, suggesting peripheral neutrophil consumption. Because of the persisting neutropenia, she was changed to adalimumab 40mg fortnightly. She was intermittently mildly neutropenic during the first 6 months, (lowest value 1.95×10⁹/l) but with a higher average neutrophil count. She currently has a normal neutrophil count and good response to adalimumab.

A 50-yr-old lady with seropositive RA requiring maintenance prednisolone (10-20mg) was intolerant of methotrexate, cyclosporin and azathioprine. She had previously documented asymptomatic neutropenia (0.42×10⁹/l) prior to commencing DMARDs, and an asymptomatic neutropenia (0.35×10⁹/l) was noted during cyclosporin treatment, rapidly responding to 10mg prednisolone. Etanercept was started and she became neutropenic (0.17×10⁹/l) 17 days after the first dose, with symptoms of sore throat, mouth ulcers and pyrexia. She was admitted for urgent intravenous tazocin and gentamicin. All cultures were negative. She required two doses of G-CSF to bring her neutrophil count over 1.0×10⁹/l. Three months later, she had a persistent neutropenia (0.61×10⁹/l), and has been maintained on 10mg prednisolone since. A bone marrow examination showed normal cellularity with active white cell production and normal granulocyte precursors.

A 61-yr-old male diagnosed in 1998 with psoriatic arthritis was intolerant of sulphasalazine. He was found to be persistently neutropenic (<2.0×10⁹/l) 17 days after the first dose, with symptoms of sore throat, mouth ulcers and pyrexia. She was admitted for urgent intravenous tazocin and gentamicin. All cultures were negative. She required two doses of G-CSF to bring her neutrophil count over 1.0×10⁹/l. Three months later, she had a persistent neutropenia (0.61×10⁹/l), and has been maintained on 10mg prednisolone since. A bone marrow examination showed normal cellularity with active white cell production and normal granulocyte precursors.

Rheumatology 2008;47:376–377
doi:10.1093/rheumatology/kem332
Advance Access publication 7 January 2008

Rheumatology key message

- A combination of RF latex plus anti-CCP antibody is an effective screening strategy for RA in primary care.

References


Three significant cases of neutropenia with etanercept

Sir, Current BSR guidelines do not recommend regular blood count monitoring for anti-TNF therapy [1] as studies have suggested no increase in adverse haematological events [2-4]. We have noted a minority (14.3%) of our patients becoming neutropenic (<2.0×10⁹/l) on anti-TNF [5], predominately asymptotically [6]. However, not all episodes have been without concern. Here we describe three cases of significant neutropenia on etanercept.

A 57-yr-old lady with aggressive seropositive RA since 1984 was intolerant of multiple DMARDs. She was on methotrexate and prednisolone (<10mg), but with persistent synovitis. An isolated episode of asymptomatic neutropenia of 1.26 during methotrexate therapy was documented. She started etanercept 25mg twice weekly, with excellent response. She became neutropenic 7 weeks after first dose (1.76×10⁹/l) and persisted throughout treatment, the lowest being 0.84×10⁹/l. These episodes responded to increased prednisolone up to 5mg. Bone marrow examination showed active haemoipoiesis and white cell production with increased immature granulocyte production, suggesting peripheral neutrophil consumption. Because of the persisting neutropenia, she was changed to adalimumab 40mg fortnightly. She was intermittently mildly neutropenic during the first 6 months, (lowest value 1.95×10⁹/l) but with a higher average neutrophil count. She currently has a normal neutrophil count and good response to adalimumab.

A 50-yr-old lady with seropositive RA requiring maintenance prednisolone (10-20mg) was intolerant of methotrexate, cyclosporin and azathioprine. She had previously documented asymptomatic neutropenia (0.42×10⁹/l) prior to commencing DMARDs, and an asymptomatic neutropenia (0.35×10⁹/l) was noted during cyclosporin treatment, rapidly responding to 10mg prednisolone. Etanercept was started and she became neutropenic (0.17×10⁹/l) 17 days after the first dose, with symptoms of sore throat, mouth ulcers and pyrexia. She was admitted for urgent intravenous tazocin and gentamicin. All cultures were negative. She required two doses of G-CSF to bring her neutrophil count over 1.0×10⁹/l. Three months later, she had a persistent neutropenia (0.61×10⁹/l), and has been maintained on 10mg prednisolone since. A bone marrow examination showed normal cellularity with active white cell production and normal granulocyte precursors.

A 61-yr-old male diagnosed in 1998 with psoriatic arthritis was intolerant of sulphasalazine. He was found to be persistently neutropenic (<2.0×10⁹/l) 17 days after the first dose, with symptoms of sore throat, mouth ulcers and pyrexia. She was admitted for urgent intravenous tazocin and gentamicin. All cultures were negative. She required two doses of G-CSF to bring her neutrophil count over 1.0×10⁹/l. Three months later, she had a persistent neutropenia (0.61×10⁹/l), and has been maintained on 10mg prednisolone since. A bone marrow examination showed normal cellularity with active white cell production and normal granulocyte precursors.
leucopenic (total white cell counts around 3.1 x 10^9/l). In 2003, his bone marrow showed active marrow and normal granulocyte precursors, and he was started on methotrexate. He demonstrated a good initial response to methotrexate 7.5 mg weekly, but this was stopped due to neutropenia of 0.9 x 10^9/l. Cyclosporin was unsuccessful (gum hypertrophy and hypertension). Methotrexate was restarted, but with persisting asymptomatic neutropenia varying between 0.57 and 0.93 x 10^9/l. Methotrexate proved ineffective for the arthritis 6 months later. He was started on etanercept. He had an excellent clinical response, but with persistent neutropenia. Six months later, he presented to clinic with weight loss and left upper quadrant pain. Total white cell count was 8.9 x 10^9/l, with neutrophils of 6.79 x 10^9/l (very high for him). Ultrasound and CT scan showed multiple splenic abscesses. Blood cultures grew Staphylococcus aureus. Despite intensive intravenous antibiotics his C-reactive protein continued to rise and repeat CT showed no improvement. He had an elective splenectomy, complicated by post-operative sepsis and bleeding requiring repeat laparotomy and a 5-day ICU stay. Splenic histology confirmed staphylococcal abscesses. He made a full recovery, and is currently well, on no medication, with normal neutrophil counts.

There have been previous reports of neutropenia with anti-TNF agents. We have found only one other report with etanercept in an ankylosing spondylitis patient, with two positive rechallenges [6]. The patient also developed neutropenia after an infliximab infusion. Agranulocytosis and neutropenia have been described with infliximab [6–8], one case requiring inpatient stay for intravenous antibiotics until the cultures were negative. A recent study of 130 patients on anti-TNF showed a cytopenia rate of 12%, mainly leucopenias, with none leading to serious infection [9].

Our first patient had no sepsis, but the second showed a rapid and dramatic neutropenia, and though cultures were negative she behaved as if septic. The third patient had pre-existing neutropenia, and developed a dramatic and life-threatening infection with staphylococcal abscesses in a most unusual location. All three patients had normal bone marrow examinations, suggesting that the neutropenia may be due to peripheral consumption rather than a primary marrow disorder. All three patients were strongly positive for IgG ANA (1/1280, 1/5120 and >1/5120, respectively), though a previous analysis showed no evidence of an association between ANA and neutropenia in RA anti-TNF patients [5]. None of the patients had symptoms of Sjögren’s syndrome. All three are negative for anti-neutrophil cytoplasmic antibodies, but we have not tested for other anti-leucocyte antibodies. The first patient has tolerated adalimumab far better than etanercept from a neutrophil perspective. The third patient has had a normal neutrophil count since his splenectomy. All three patients had episodes of neutropenia prior to their anti-TNF treatment, which significantly worsened with etanercept. We advise that all patients on anti-TNF agents should be monitored with regular full blood counts, with particular care for those with previously documented neutropenia [5]. We are not alone in this recommendation [9].

**Rheumatology key message**

- Etanercept can be associated with significant neutropenia.

**Disclosure statement:** The Department of Rheumatology at Derbyshire Royal Infirmary has received sponsorship from Wyeth, Abbott and Schering Plough Pharmaceuticals for support of clinical meetings, and unrestricted grants from Wyeth and Schering Plough to support an anti-TNF audit clerk and research nurse. K.G. sits on an advisory board for Schering Plough, and has received honoraria for talks at symposia sponsored by Wyeth and Abbott. C.D. has previously sat on an advisory board for Schering Plough and received honoraria for talks at symposia sponsored by Wyeth and Abbott. All other authors have declared no conflicts of interest.

C. WENHAM, K. GADSBY, C. DEIGHTON

Department of Rheumatology, Derbyshire Royal Infirmary, Derby, DE2 2QY, UK

Accepted 14 November 2007

Correspondence to: C. Deighton, Department of Rheumatology, Derbyshire Royal Infirmary, Derby, DE2 2QY, UK. E-mail: chris.deighton@derbyhospitals.nhs.uk

4 Ang H, Heffegod S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumour necrosis factor-alpha antagonists in patients with rheumatoid arthritis? J Rheumatol 2003;30:2315–8.

Rheumatology 2008;47:377–378
doi:10.1093/rheumatology/kem361

Advance Access publication 22 January 2008

**Cholesterol crescents and plates in shoulder effusion of a rheumatoid patient**

Sir, While the occurrence of cholesterol effusions in patients with inflammatory arthropathy is a recognized phenomenon, the aetiology of this complication is not known. Whether there is any relationship to hyperlipidaemia remains speculative although a previous report has described clinical response to statin therapy [1]. We would like to report our experience of a patient with seronegative, erosive rheumatoid arthritis, whose disease was unresponsive to sequential DMARD combination therapy and also to oral steroid/DMARD combination treatment. In June 2005, he was commenced on etanercept and methotrexate combination therapy but stopped it perioperatively in December 2006 whilst he underwent knee replacement surgery. Later that month, he developed a large left shoulder effusion and aspiration yielded cholesterol crescents (Fig. 1). The finding of cholesterol crescents is rare in inflammatory arthropathy is a recognized phenomenon, the aetiology of this complication is not known. Whether there is any relationship to hyperlipidaemia remains speculative although a previous report has described clinical response to statin therapy [1]. We would like to report our experience of a patient with seronegative, erosive rheumatoid arthritis, whose disease was unresponsive to sequential DMARD combination therapy and also to oral steroid/DMARD combination treatment. In June 2005, he was commenced on etanercept and methotrexate combination therapy but stopped it perioperatively in December 2006 whilst he underwent knee replacement surgery. Later that month, he developed a large left shoulder effusion and aspiration yielded cholesterol crescents (Fig. 1). The finding of cholesterol crescents is rare and they usually occur only in shoulder effusions. Fasting serum cholesterol was normal.

He was commenced on simvastatin 20 mg daily in February 2007 and methotrexate was switched to subcutaneous administration at a dose of 7.5 mg/week in March 2007. There was no improvement in disease status or in the shoulder effusion. His CRP was 41 mg/l. In May 2007, he suffered a further disease flare and oral prednisolone was increased from 5 mg daily to 20 mg daily temporarily. This resulted in an excellent clinical response.