The safety and efficacy, and recommendations for the use of biologic drugs in the UK military rheumatology population

Alexander N Bennett,[1,2] A D Green,[3] J Rees,[1] T Jones,[1] D Harris,[1] J Etherington[1]

[1]Department of Rheumatology, Defence Medical Rehabilitation Centre, Headley Court, Surrey, UK
[2]Academic Centre for Musculoskeletal Medicine, University of Leeds, Leeds, UK
[3]Royal Centre for Defence Medicine, Birmingham, UK

Correspondence to
J Etherington,
Department of Rheumatology, DMRC Headley Court, Epsom, Surrey KT18 6JW, UK; Dmrc-directordefencerehabilitation@mod.uk

To cite: Bennett AN, Green AD, Rees J, *et al*. *J R Army Med Corps* 2013;**159**:8–14.

ABSTRACT

Inflammatory arthritis is a significant cause of morbidity in the military. In particular the sero-negative spondyloarthritides, which include ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory bowel disease related arthritis and undifferentiated spondyloarthritis, are especially prevalent in the young male phenotype, which is common in the Armed Forces. It is estimated that there are more than 1500 patients in the Armed Forces with spondyloarthritis alone, based on the prevalence in the general population of approximately 1%. Inflammatory arthritides are eminently treatable, especially with the development and widespread use of biologic drugs such as anti-Tumour Necrosis Factor (TNF) therapy. The use of these drugs can deliver patients an exceptionally good outcome leading to symptom control and normal function in many cases. Initial concerns regarding safety and side effects of anti-TNF drugs have been allayed by the evidence provided from comprehensive national databases developed over the last 10 years. With early diagnosis and prompt treatment military patients can complete a full career including deployment with only minor limitations. This paper reviews the burden of inflammatory arthritis in the armed services, its management and outcome in this population, the evidence for the safety of anti-TNF treatments and the recommendations for employability and deployability for service personnel.

Educational points

- Anti-TNF drugs are highly effective and very safe in the treatment of inflammatory arthritis
- Anti-TNF drugs are particularly safe in young spondyloarthritis patients with minimal co-morbidity and polypharmacy, as is often the case with Armed Services patients.
- With appropriate specialist review Armed Services personnel on anti-TNF may still be deployed in restricted roles with appropriate limitations

INTRODUCTION

Inflammatory arthritis causes significant morbidity in the Armed Forces. The treatment and outcome of inflammatory rheumatic disease has been revolutionised with the introduction of biologic drugs as part of routine clinical practice. These drugs are being used, in combination with traditional treatments, in military patients resulting in excellent functional outcomes and increased employability and deployability in rheumatic conditions that previously had a poor or moderate prognosis.

The first generation anti-Tumour Necrosis Factor (TNF) drugs were introduced into clinical practice at the beginning of the last decade. These changed the lives of patients with severe inflammatory rheumatic disease, which often resulted in severe chronic disease, structural damage and functional and vocational impairment. Rheumatologists were previously managing these conditions with non-targeted, non-specific disease modifying anti-rheumatic drugs with a variable outcome.[1] Initially licensed for the use in rheumatoid arthritis (RA) it was soon recognised that the anti-TNF drugs were even more effective in seronegative spondyloarthritides such as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and inflammatory bowel disease-related arthritis. Inflammatory arthritides, particularly the seronegative spondyloarthritides (SpA) as a whole, are common in the Armed Forces where the population is young and predominantly male, both of which are classical features of these conditions. However, there was initial concern regarding the safety of these drugs, given that they are given long term and interfere with the innate immune system. In this article we review the efficacy and safety of anti-TNF drugs, in particular relation to the Armed Forces patient population and give our evidence-based recommendations on medical employment and deployment standards.

INFLAMMATORY ARTHRITIS IN THE ARMED SERVICES

The Armed Services have many patients with inflammatory rheumatological conditions with approximately 150–200 new cases being diagnosed each year and the predominant inflammatory conditions are the SpAs. The prevalence of SpA as a group in the general population is 1%, so it is estimated that there are over 1500 patients with SpA currently serving in the Armed Services. With the services population demographics being biased towards the young and male it is likely that the number is greater, and exact data are currently being collated.Prior to the introduction of anti-TNF therapy patients have been medically downgraded depending on the degree of functional disability or medical complications of these conditions, but generally treatment had no, or limited, direct affect on the medical category.

The Armed Forces and Defence Medical Rehabilitation Centre (DMRC) Headley Court has a long tradition of treating inflammatory arthritis and

has been at the forefront of exercise-based therapy for these patients. The ASPIRE (Ankylosing Sponydylitis Inpatient Rehabilitation and Education) programme is offered to patients with axial-SpA and AS. Despite group exercise rehabilitation being widely recognised and supported by Cochrane database evidence[2–4] as essential in the treatment axial-SpA and AS, DMRC Headley court is one of only two facilities that offers this programme in the UK, the Royal National Hospital for Rheumatic Diseases in Bath being the other. Traditionally, in-patient rehabilitation has been combined with medication in the treatment of axial disease. The rehabilitation targets range of movement and function with a consequent positive effect on vocational outcome, well-being and quality of life. The traditional drug treatments for axial symptom control have been non-steroidal anti-inflammatories (NSAIDS)[5–7] but these are inadequate in 50% of the patient population and have no convincing disease modifying effect. Service and Ministry of Defence (MOD) Rheumatologists are now managing these patients with the combination of anti-TNF drugs and in-patient rehabilitation, which again is a unique position nationally. DMRC outcome data confirms the impression that these patients are getting excellent symptomatic and functional outcomes.[8]

BIOLOGIC DRUGS FOR INFLAMMATORY ARTHRITIS IN THE ARMED SERVICES

Since the introduction of biologic drugs in the NHS in the last decade anti-TNF therapies have been used in Armed Forces personnel with inflammatory rheumatic conditions. Initially this was for RA with the National Institute for health and Clinical Excellence (NICE) approval of first generation anti-TNF therapies in 2002, but their use has escalated rapidly with the subsequent NICE approval of anti-TNF therapies in psoriatic arthritis in 2006 and AS in 2008.In PsA and AS, the two commonest forms of SpA in the services, there have been multiple controlled trials,[9–16] proving their efficacy and demonstrating a dramatic effect on symptoms - often resulting in the patient becoming asymptomatic and fully functional, but requiring regular treatment.

These drugs were first used in military patients in 2006 at DMRC, Queen Alexandra Hospital Portsmouth and occasionally in other civilian rheumatology practices. Data from DMRC confirms excellent results in the 64 patients who have been on the drugs.[8] Initially due to early concerns regarding the potential side effects[17–19] of the drugs these patients have been graded P7 MND (Medically Non-Deployed) or its equivalent. A overview of the efficacy and safety of anti-TNF in the military cohort is described here with a more detailed review of current evidence on anti-TNF side effects.

Efficacy

Since January 2006, 64 military patients have been started on anti-TNF for AS (35), PsA(18), RA (10) and a single other patient. The mean age of these patients is 37 years indicating a cohort of patients with significant military experience and training, but still with time left to serve. Of these 64 patients only four (6.25%) have been medically discharged due to their inflammatory arthritis. The remaining 60 patients are able to complete significant military roles with minor functional restrictions.

The military AS cohort, the largest of the inflammatory arthritis groups and recognised to generally have the best, most consistent response to anti-TNF therapy, have had an excellent response and outcome.[8] The mean baseline disease activity measure, the Bath Ankylosing Spondylitis Activity Index (BASDAI), which is measured on a 0–10 score, for this group was 6.93 (range 4.08–9.6) indicating severe disease activity (Figure 1). The response to anti-TNF has been excellent with a mean post anti-TNF BASDAI of 2.11 (range: 0.3–5.83) indicating low levels of disease with a mean absolute improvement of 4.96 (range: 1.26–9.33) and a mean percentage improvement of 70% (range: 15–98). All of these patients met NICE and British Society for Rheumatology (BSR) guidelines for anti-TNF eligibility and 94% meeting NICE/BSR guidelines for response to treatment. Defence rheumatologists have the ability and experience to diagnose these patients early[20 21] and where appropriate treat early in the disease process[22] which along with young age is a predictor of good response to anti-TNF treatment.[23]

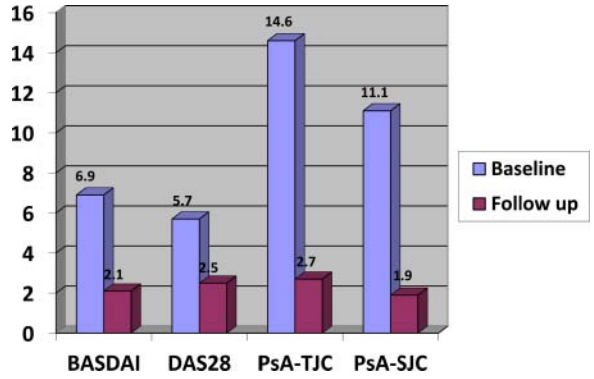

Figure 1 Mean outcomes in 64 patients with inflammatory arthritis in the Armed Forces on anti-TNF therapy. BASDAI (Bath Ankylosing Spondylitis Activity Index (range 0–10)); DAS28 (Disease Activity Score 28 joint count for Rheumatoid Arthritis (range 0–9)); PsA-TJC (Psoriatic Arthritis Tender Joint Count (0–68)); PsA-SJC (Psoariatic Arthritis Swollen Joint Count (0–66)).

In the PsA group of 18 patients, the cohort had severe disease with a pre anti-TNF mean tender joint count (TJC) and swollen joint count (SJC) 14.6 (range: 2–41) and 11.1 (range: 2–24) respectively. Again the response to treatment with anti-TNF has been excellent with post anti-TNF mean TJC 2.8 (2–14), mean change in TJC 13.2 (1–41) and mean SJC 1.85 (0–17) with a mean change of 9.9 (0–24). All met NICE/BSR eligibility criteria for starting anti-TNF and 94% met the NICE/BSR response criteria.

Due to the demographic of the military population the RA anti-TNF cohort is the smallest of the inflammatory arthritis subgroups. The 10 patients (mean age: 39.5 years (26–48)) have a mean pre-anti-TNF Disease activity score (DAS28) 5.71 (5.29–6.41), with a post-anti-TNF DAS28 of 2.50 (1.2–3.77) with a DAS28 of <2.6 indicating clinical remission. The absolute change in DAS28 was 3.15 (1.2–3.3) with a change of >1.2 indicating a good EULAR (European League Against Rheumatism) response.

Overall in the military treated anti-TNF patients there has been an excellent response with minimal side effects, which are better than those reported in key randomised controlled trials in these conditions.[12 24]This is likely to be because of the younger age group and the reduced co-morbidities and polypharmacy in the military compared to civilian populations. Importantly, in our cohort the improved disease activities are associated with improved functional and occupational outcomes.

SAFETY

So far in five years of prescribing in 64 patients there have only been two significant adverse events. One was a rash associated

with starting adalimumab that required cessation of the drug and the other was a transient otherwise unexplained rise in liver enzymes which settled with temporarily withholding the drug with no recurrence on restarting.

DEPLOYMENT

Three 'test' cases of servicemen undergoing treatment with anti-TNF have already been deployed to main operating bases in Afghanistan without incident. Two continued with anti-TNF treatment and one had a 'drug holiday' during the deployment, recommencing treatment on return without detriment. In each case the disease has been extremely well controlled with the anti-TNF drugs resulting in minimal symptoms and excellent function. The rheumatology cadre, in conjunction with the Defence Consultant Adviser (DCA) in Communicable Diseases, have now completed an evidence-based review and agree that there is now sufficient evidence to recommend a Joint Medical Employment Standard (JMES) for these patients that allows deployment with some limitations.

SAFETY OF BIOLOGIC DRUGS

Increasing and widespread use of biologic drugs, in particular anti-TNF therapies, has improved the knowledge and understanding of their efficacy and in particular safety, through many national and international registries, in particular the British Society for Rheumatology Biologics Register (BSRBR) which is the largest and has data on over 19 000 patients. The general consensus is that the initial concerns over potential risks of the drugs, in particular infection, are much less than originally thought.[25]

Summary of Literature Review of anti-TNF Safety and Prescribing

The BSRBR[25] is a British registry started in 2001 compiling over 19 000 patients in the UK with RA treated with any of the three first generation anti-TNF therapies infliximab, etanercept or adalimumab. An observational study from the registry found no significant difference in serious infections between anti–TNF group (53.2 per 1000) and control group (disease modifying anti-rheumatic drugs (DMARDs) treated patients).[25] However further analysis did indicate an increased risk of skin and soft tissue infections with an incidence rate ratio (IRR) of 4.2. Sub-analysis also revealed a possible risk in early stages of treatment.[26] A similar Spanish Biologics registry[27] compared 2868 patient years for anti-TNF v 2433 patient years for controls and found only a small increase in relative risk (1.6) for serious infection. A small German registry[28] of 858 anti-TNF patients were compared to DMARD-treated controls and found an increase in relative risk of serious infection of 2.2. All data demonstrated a noticeably lower relative risk of infection in this population than was expect at the outset. The largest, the British database, overall shows no increase in infection and our clinical data over six years supports these finding.

A limitation of using such registries for evidence in military populations is that they are compiled from RA patient data, whereas anti-TNF drugs are predominantly used in the British military for SpA. That said, the safety of the drug in military patients may be better, as the patients are younger[26] and otherwise healthy with less poly-pharmacy and fewer co-morbidities compared to RA database patients. Furthermore there is evidence from the national registries that the infection risks for RA (RR: 4.1) are notably higher than in SpA (PsA: 2.1, AS: 1.2).[29] Although these databases have the best evidence available on infection risk in anti-TNF treated patients another limitation is the comparator control groups being DMARD-treated patients rather then 'true' healthy controls. The risk therefore is a relative risk rather than absolute. That said, there are many studies indicating that there is no increased risk of infection with low dose methotrexate (the commonest used DMARD) in rheumatoid treated patients,[30–37] justifying this group as a control group.

CURRENT INFECTION RISKS IN AFGHANISTAN

The risk of acquiring a communicable disease is determined by a variety of different factors, relating both to the disease and the host. Most infections classed as 'Tropical Diseases' are in fact found more commonly in exotic climates because of social and environmental factors rather than geographical locations. For example many infections are related to poor housing and overcrowding, contaminated water supplies and inadequate sanitation, and lack of access to basic medical supplies. However there are some that are associated with climate, including many of the vector-borne diseases that are dependent on complex host-parasite interactions.

It is important to consider these first principles when trying to determine the risk of exposure to infectious diseases for individuals who are immunosuppressed, such as those taking anti-TNF. The risk assessment should take account not only of geographical location, but more detailed evaluation of exposure risks (Table 1).

Current operational deployments vary enormously, and it is therefore important to try to accurately determine the risk of exposure to infection for each individual case. Such servicemen are often highly trained and valued professionals, and making best use of their skills is appropriate both for the individuals and the military organisation. For example, the risk of an individual from infectious diseases on being posted to a major base in Afghanistan is likely to be no greater than that in the UK

Table 1 Factors that need to be considered in medical risk assessment for infection on deployment

Risk Assessment Measure	Example
Presence or absence of vector-borne diseases	
Vector control measures in place	Fogging for adult insects, larvicide use, residual insecticides on accommodation
Individual bite prevention strategies	Availability of repellents, impregnated bed nets and clothing
Physical infrastructure	Screened air-conditioned accommodation versus tentage
Evaluation of accommodation	Respiratory disease transmission in barrack blocks or transit tents
Water supply	Bottled, secure bore hole, or filtered river water
Sanitation	Deep trench latrines or improvised sewage disposal at Patrol Bases, or piped toilets at Major Operating Bases
Food supply	Shared local meals for embedded personnel, or formal catering establishments in main camps

since the incidence of infectious disease in the local population will be similar to that at home, as will the living conditions. Indeed any soldier in a major base area will have ready access to primary and tertiary medical care at his location and hence early diagnosis and management. In contrast, the risk to the same individual posted to the same geographical region but in a forward role would be quite different, where the factors for disease transmission described above are likely to be present.

Data for rates of infectious diseases in geographical locations need to be interpreted with insight and caution. For a deployed Military Force there is generally significant medical selection and preparation. This ranges from initial selection procedures, monitoring of basic health and fitness by occupational medical support, public health immunisations for diseases associated with military service, immunisations for diseases related to overseas travel and occupational risk, and core military training with respect to field hygiene and personal welfare. In addition a formed military unit will also have Force Health Protection measures in place, including food and water security, vector control measures, and environmental health specialist support. In contrast, local populations overseas may have none of the health and environmental infrastructure, and the rates of disease may be markedly different. In Afghanistan in 2011 the rates of illness in major bases are broadly comparable to those in Western cities, whilst rates of some diseases such as gastrointestinal disease and skin disease are more common in forward locations.[38] This contrasts with the experiences of occupying Soviet Forces in the 1980s, which had little food and water security, no environmental health support and were broadly dependent on the local economy. Throughout that campaign over 60% of the Force were hospitalised at some time, and there were large outbreaks of Sandfly Fever, Hepatitis A and malaria.[39] These diseases remain endemic in the region, but effective control measures mean that they account for only a small number of cases each year in NATO personnel.[40]

Tuberculosis is an infection of particular concern for individuals who are immunosuppressed when taking anti-TNF. However the increased risk is mainly associated with reactivation of old infection,[17 18] as is seen in other immunosuppressive conditions.Tuberculosis is very uncommon in service personnel and all service personnel prescribed anti-TNF are thoroughly screened for active and latent tuberculosis with chest x-ray (CXR) and quantiferon gold (interferon γ release assay).There is a higher risk of tuberculosis associated with some anti-TNF agents (Infliximab & adalimumab) than others (etanercept).[17 18 41 42] However it should be stressed that these studies include a markedly different population than those in the British Armed Forces and therefore the risk is considered to be much lower.

Deployed Armed Services personnel may be in working contact with Afghan locals or contractors from the Indian subcontinent where tuberculosis rates are higher. However new acquisition of tuberculosis requires intimate close contact over a prolonged period with another individual who is shedding large numbers of bacteria by the respiratory route ('smear-positive open tuberculosis'). Even then, the disease is difficult to acquire-the rate of disease transmission to susceptible household contacts over extended exposure periods is of the order 10% from cases who are demonstrated to be 'highly infectious'.[43] Contact tracing following identification of a case is generally only confined to household extended contacts, and rarely extended beyond this group because the rates of transmission are so low.[44]

In the operational context, this means that an individual living and working in a major base is unlikely to be exposed to tuberculosis any more than in his home environment. Coalition personnel are actively examined for this disease, and report sick when symptomatic. Locally employed civilian personnel will not be working while ill with clinical tuberculosis and any who are infected but without symptoms will not be infectious to others. There are also civilian contractors employed who originate from countries with high rates of tuberculosis, but they too will be not be working while symptomatic and infectious to others. There is extensive evidence collected from around the world to indicate that acquisition of tuberculosis in the occupational setting is extremely uncommon, and that casual exposure to individuals with active tuberculosis carries a very low risk of disease acquisition.[44]

Therefore the risk of reactivation of latent tuberculosis in military personnel is low and the risk of new acquisition of tuberculosis in deployed personnel on anti-TNF therapy is also likely to be low. As in NHS care, military patients are given a choice of treatments. However, due to differences in tuberculosis data with the different anti-TNF drugs, as mentioned above, unless there is a clinical indication for other agent's, etanercept is recommended to be used as the first line anti-TNF in service personnel due to its lower risk of tuberculosis infection and its shorter half-life.

MANAGEMENT OF ANTI-TNF PATIENTS AND JOINT MEDICAL EMPLOYMENT STANDARDS RECOMMENDATIONS

All military personnel are given a JMES, which indicates their ability to perform their designated military role and other general military tasks. Of particular relevance are the deployability recommendations, which determine an individual's ability and suitability from a medical perspective to perform their job in an operational theatre. Previously patients with inflammatory arthritides treated with anti-TNF therapy were automatically considered to be medically non-deployable. However the Directorate of Defence Rehabilitation has reviewed current literature on the safety of anti-TNF drugs, as summarised above, and has liaised closely with DCA in Communicable Diseases on conditions and infection risks in Afghanistan and has made JMES recommendations for these patients (Box 1).

RHEUMATOLOGICAL MANAGEMENT OF PATIENTS ON ANTI-TNF THERAPY TO REDUCE RISK OF FUTURE INFECTION

The Defence rheumatology management of all military patients on anti-TNF drugs is based on an evidence base review of safety of anti-TNF drugs completed by the British Society for Rheumatology[45] with an aim of minimising risk in these patients.It is standard practice for military and MOD Rheumatologists to fully screen all patients prior to starting therapy. Standard definitions of levels of evidence (I –IV) and grade of recommendations were used (A-D).[46] This includes screening for previous TB exposure (Level of evidence: IIb, Grade of recommendation B)[45] to include history of TB exposure, CXR and quantiferon gold test. Patients are also screened for HIV (III, B)[45] and hepatitis (IV, B)[45] risk and if the patients are high risk then serum samples are tested to exclude the diseases. Immunisation records are checked and all essential vaccinations are recommended prior to the commencement of anti-TNF if not currently in date. Future live attenuated vaccines such as yellow fever require cessation of anti-TNF for 3 months before and 1 month after vaccination (recommendations of Arthritis Research UK). If previous chicken pox is in any doubt

Box 1 Joint Medical Employment Standard (JMES) Rheumatology Cadre Recommendations for Anti-TNF (Tumour Necrosis Factor) treatment of Inflammatory Arthritis. MOD (Ministry of Defence); MND (Medically Non Deployable); MLD (Medically Limited deployability); TB (Tuberculosis).

Recommendations

- Patients with inflammatory arthritic conditions requiring treatment with anti-TNF therapy should all be reviewed by a service/MOD consultant rheumatologist and recommended an appropriate JMES.
- Patients with medical complications or functional impairment, due to their disease, resulting in vocational limitations, should have JMES recommendations appropriate to their clinical and functional condition.
- Patients who are started on anti-TNF therapy should be temporarily downgraded P7 MND for 12 months.
- Etanercept should be the first choice anti-TNF, unless there are clinical indications for other anti-TNF drugs, as it has a reduced TB infection risk and a shorter half-life.
- Patients with these inflammatory arthritis conditions who are stable with no side effects to anti-TNF, asymptomatic and fully functional after 12 months of anti-TNF therapy should have a recommended JMES:
  A. P3* MLD
  B. Caveats:
     1. Base areas only ie Bastion/ Khandahar/Kabul
     2. be made available for regular medical review (restriction code 415)
     3. No prolonged daily very close physical contact ('household' contact) with Afghan nationals or other populations where TB is endemic.

  *Patients who are stable with no side effects to anti-TNF but have mild/moderate symptomatology or functional restriction can be considered for P7 MLD.
- Patients on anti-TNF should be clinically reviewed prior to any deployment and routinely six monthly by their consultant rheumatologist to include an assessment of their JMES.

then immunity is checked and vaccination is recommended if necessary (IV, C).[45] Anti-TNF therapy does not effect malaria prophylaxis recommendations.[47] Finally patients are educated regarding food hygiene (III, B)[45] and three monthly blood monitoring is instigated as recommended by the BSR.

MEDICAL MANAGEMENT OF PATIENTS ON ANTI-TNF WHO HAVE INFECTION

Even though the overall increased risk of infection has been demonstrated to be less than initially thought, patients on anti-TNF can obviously still develop infections. In the event of infections other than mild viral illness, anti-TNF should be stopped and the infection should be treated. The anti-TNF can be restarted once infection has clinically resolved (III, B).[45] In the event of a varicella infection the anti-TNF drug should be stopped and VZIG (Varicella Zoster immunoglobulin) given (IIb, B).[45]

In the event of major trauma or any other medical event that increases the risk of infection the anti-TNF should be stopped immediately and the patient treated as clinically appropriate. In the cases of elective operations treatment should ideally be stopped three to five half lives before the operation with the half lives of etanercept, infliximab, adalimumab being 70 h, 8–9.5 days, and 12–14 days respectively.

PROVISION OF TREATMENT FOR INFLAMMATORY ARTHRITIS WITHIN THE ARMED SERVICES

The rheumatology and rehabilitation cadre have a 'hub and spoke' service for the management of inflammatory

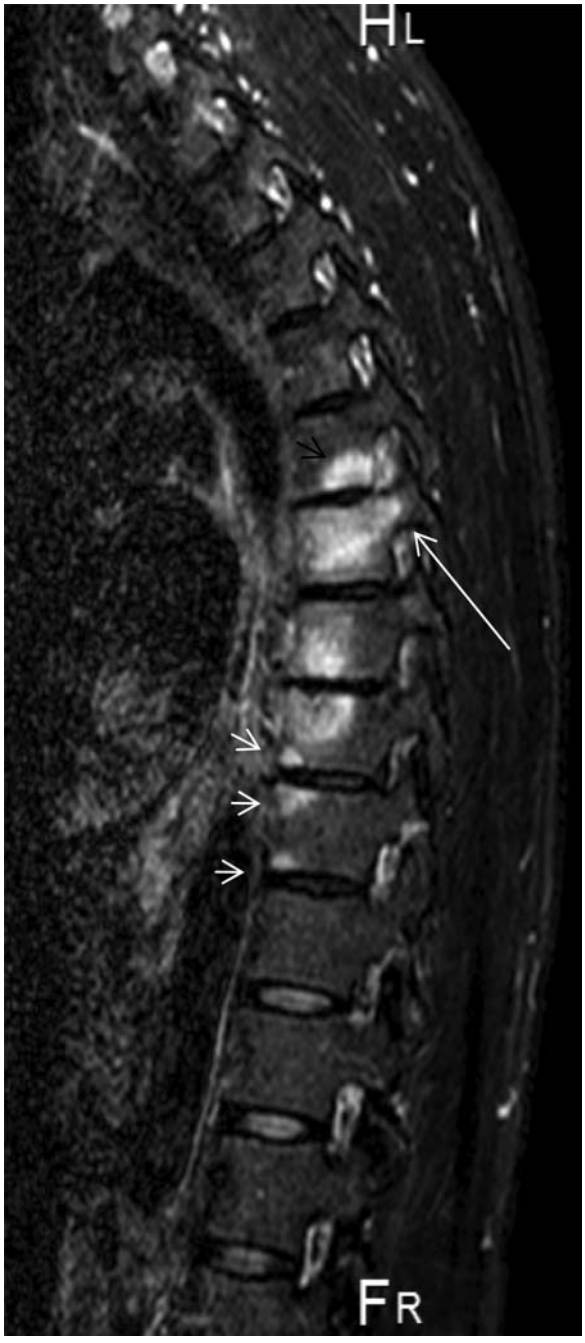

Figure 2 STIR (Short Tau inversion recovery) sequence sagittal MRI of the spine in a 40yr old male soldier with a diagnosis of Psoriatic- axial Spondyloarthritis. Radiographs were normal. Posterior element lesion (white arrow), and multiple inflammatory Romanus lesion (arrow heads) confirm the early diagnosis.

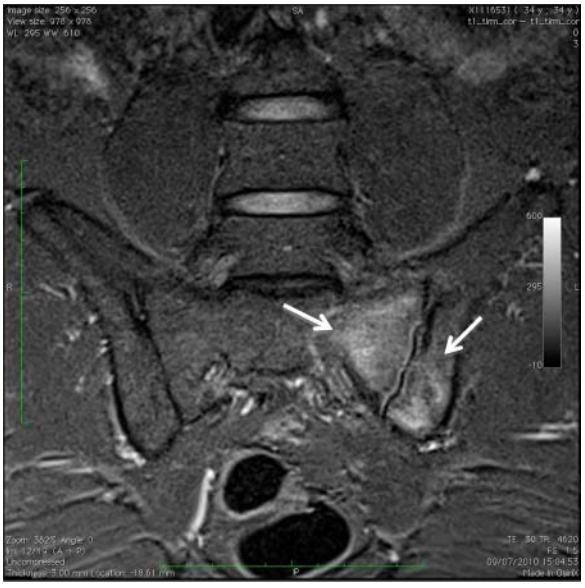

Figure 3 STIR sequence MRI of the sacroiliac joints (SIJs) in a 38 yr old male with a 4 month history of inflammatory back pain with normal x-rays. MRI confirms classical left sided active sacroiliitis with high signal subchondral bone marrow oedema (left severe, arrows) confirming the early diagnosis of axial-SpA.

rheumatology and offer assessment, early diagnosis and treatment with regular review with an aim to achieving excellent outcomes. The two hubs are the inflammatory arthritis service at DMRC Headley court and the military rheumatology service at Portsmouth Ministry of Defence Hospital Unit (MDHU). Initial assessment, investigation, diagnosis and management are performed. These rheumatology services provide rapid access for new patient referrals, on site musculoskeletal ultrasound in the inflammatory arthritis clinic, excellent access to other imaging including Magnetic Resonance Imaging (MRI) which are essential for early diagnosis (Figures 2 and 3), access to all standard medical treatments and importantly access to one of only two inpatient rehabilitation courses for SpA in the UK. Subsequently, if the patients are well controlled and stable on treatment they may be followed up in one of the regional Defence Rheumatology Clinics (DRCs) if more geographically convenient. These DRCs include Guy's Hospital London, Catterick Garrison and Edinburgh Medical Reception Station (MRS).

All military patients with suspected or confirmed inflammatory arthritis should be managed within the Defence Rheumatology services, as outlined above, rather than the NHS. The Defence Rheumatology cadre provides a comprehensive healthcare system and allows continuity of care despite change of location with posting and informed vocational and employability and deployability advice with regards to the inflammatory conditions and treatments. There is always a DMRC consultant available via the DMRC switchboard (01372 378271) to advise on any aspect of the management of patients with inflammatory arthritis.

CONCLUSION

Biologic therapy is a huge step forward in the management of inflammatory arthritis and anti-TNF therapy for the treatment of the spondyloarthropathies and their associated excellent outcomes are of particular relevance to the Armed Services. Patients diagnosed with inflammatory arthritis are now, more than ever, eminently treatable, and in the Armed Services young and often otherwise fit patients treated with traditional or new biologic treatments, frequently achieve excellent outcomes with full function. The latest evidence from years of data on thousands of patients on anti-TNF suggests that risks are less that initially thought. With the recommendations detailed in this paper Armed Service personnel can often continue a fully functional career including appropriate deployments.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Zochling J, Bohl-Buhler MH, Baraliakos X, *et al*. Nonsteroidal anti-inflammatory drug use in ankylosing spondylitis-a population-based survey. *Clin Rheumatol* 2006;25:794–800.
2 Kraag G, Stokes B, Groh J, *et al*. The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis–a randomized controlled trial. *J Rheumatol* 1990;17:228–33.
3 Dagfinrud H, Kvien TK, Hagen KB. The Cochrane review of physiotherapy interventions for ankylosing spondylitis. *J Rheumatol* 2005;32:1899–906.
4 Elyan M, Khan MA. Does physical therapy still have a place in the treatment of ankylosing spondylitis? *CurrOpinRheumatol* 2008;20:282–6.
5 Song IH, Poddubnyy DA, Rudwaleit M, *et al*. Benefits and risks of ankylosing spondylitis treatment with nonsteroidalantiinflammatory drugs. *Arthritis Rheum* 2008;58:929–38.
6 van der Heijde D, Baraf HS, Ramos-Remus C, *et al*. Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005;52:1205–15.
7 Jarrett SJ, Sivera F, Cawkwell LS, *et al*. MRI and clinical findings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. *Ann Rheum Dis* 2009;68:1466–9.
8 Rees J, Bennett AN, Harris D, *et al*. Early intervention with Anti-TNF therapy in ankylosing spondylitis with young age and short disease duration produces superior clinical results in standard clinical practice. *Ann Rheum Dis* 2011;70(Suppl 3):337.
9 Brandt J, Haibel H, Cornely D, *et al*. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2008;43:1346–52.
10 Brandt J, Khariouzov A, Listing J, *et al*. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003;48:1667–75.
11 Brandt J, Listing J, Haibel H, *et al*. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. *Rheumatology (Oxford)* 2005;44:342–8.
12 Braun JB. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicentre trial. *Lancet* 2002;359:1187–93.
13 Braun JB. Two- year maintenance of efficacy and saftey of infliximab in the treatment of ankylosing spondylitis. *Ann Rheum Dis* 2005;64:229–34.
14 Braun J, Baraliakos X, Brandt J, *et al*. Persistent clinical response to the anti-TNF-alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. *Rheumatology (Oxford)* 2005;44:670–6.
15 van der Heijde D, Da Silva JC, Dougados M, *et al*. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006;65:1572–7.
16 van der Heijde D, Dijkmans B, Geusens P, *et al*. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;52:582–91.
17 Gomez-Reino JJ, Carmona L, Valverde VR, *et al*. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003;48:2122–7.
18 Wallis RS, Broder MS, Wong JY, *et al*. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004;38:1261–5.
19 Curtis JR, Patkar N, Xie A, *et al*. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum* 2007;56:1125–33.
20 Bennett AN, McGonagle D, O'Connor P, *et al*. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008;58:3413–8.
21 Bennett AN, Rehman A, Hensor EM, *et al*. Evaluation of the diagnostic utility of spinal magnetic resonance imaging in axial spondylarthritis. *Arthritis Rheum* 2009;60:1331–41.

22 Barkham N, Keen HI, Coates LC, *et al*. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum* 2009;60:946–54.
23 Rudwaleit M, Listing J, Brandt J, *et al*. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:665–70.
24 van der Heijde D, Kivitz A, Schiff MH, *et al*. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006;54:2136–46.
25 Dixon WG, Watson K, Lunt M, *et al*. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;54:2368–76.
26 Galloway JB, Hyrich KL, Mercer LK, *et al*. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011;50:1341–2.
27 Carmona L, Descalzo MA, Perez-Pampin E, *et al*. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. *Ann Rheum Dis* 2007;66:880–5.
28 Listing J, Strangfeld A, Kary S, *et al*. Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum* 2005;52:3403–12.
29 Burmester GR, Mease P, Dijkmans BA, *et al*. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis* 2009;68:1863–9.
30 Franklin J, Lunt M, Bunn D, *et al*. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. *Ann Rheum Dis* 2007;66:308–12.
31 Doran MF, Crowson CS, Pond GR, *et al*. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002;46:2294–300.
32 Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006;54:628–34.
33 Smitten AL, Choi HK, Hochberg MC, *et al*. The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol* 2008;35:387–93.
34 Coyne P, Hamilton J, Heycock C, *et al*. Acute lower respiratory tract infections in patients with rheumatoid arthritis. *J Rheumatol* 2007;34:1832–6.
35 McLean-Tooke A, Aldridge C, Waugh S, *et al*. Methotrexate, rheumatoid arthritis and infection risk: what is the evidence? *Rheumatology (Oxford)* 2009;48:867–71.
36 Lacaille D, Guh DP, Abrahamowicz M, *et al*. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;59:1074–81.
37 Edwards CJ, Cooper C, Fisher D, *et al*. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. *Arthritis Rheum* 2007;57:1151–7.
38 DASA DASAA. Defence Analytical Services and Advice (DASA), Ministry of Defence British Casualties – Afghanistan Edition. 2011. http://www.dasa.mod.uk/Afghanistan Edition - 07 Oct 01–30 Jun 11 (accessed 14 Oct 2011).
39 Sergiev VP BAOVEA. Importation of malaria into the USSR from Afghanistan, 1981–89. *Bull World Health Organ* 1993;71:385–8.
40 Bailey MS, Trinick TR, Dunbar JA, *et al*. Undifferentiated febrile illnesses amongst British troops in Helmand, Afghanistan. *J R Army Med Corps* 2011;157:150–5.
41 Dixon WG, Hyrich KL, Watson KD, *et al*. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2009;69:522–8.
42 Tubach F, Salmon D, Ravaud P, *et al*. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum* 2009;60:1884–94.
43 Gryzbowski S BGSK. Contacts of cases of active pulmonary tuberculosis. *Bull Int Union Tuberc* 1975;50:90–106.
44 National Institute for Clinical Excellence. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. 2011.
45 Ding T, Ledingham J, Luqmani R, *et al*. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. *Rheumatology (Oxford)* 2010;49:2217–9.
46 http://www.nice.org.uk/niceMedia/pdf/GDM_Chapter7_0305.pdf (accessed 21 July 2012).
47 Orenstein R. Travel in patients receiving TNF-alpha inhibitors. Travel Med Infect *Dis* 2005;3:105–9.