The finding that aberrant TGF-β signalling was involved in the pathogenesis of LDS prompted Loeys et al. [4] to investigate the role of TGF-β in MFS. It emerged that increased TGF-β levels and activity was evident in preclinical models and patients with MFS, a phenomenon explained by the fact that TGF-β is normally sequestered (and regulated) in the extracellular matrix by binding to fibrillin [7]. Moreover, suppression of TGF-β in preclinical models and individuals with MFS led to disease arrest [8-10]. This was achieved either by administration of TGF-β1-neutralizing antibodies or by delivery of angiotensin II antagonists, which, through reasons that are incompletely understood, are able to suppress TGF-β levels. Indeed, Losartan prevented aortic aneurysm development in an MFS mouse model [8] and delayed aortic root enlargement in 18 children with MFS [9]. Perindopril was shown to reduce aortic root measurements and improve arterial compliance in adult patients with MFS [10]. Several large randomized controlled trials are ongoing across the USA and Europe.

Management of LDS involves regular MRA surveillance scans to establish the extent of vascular involvement, early surgical intervention, genetic counselling and monitoring in pregnancy. TGF-β antagonism with angiotensin II receptor blockers is recommended, as this may confer a similar protective effect to that observed in MFS. Our case emphasizes the importance of considering LDS in the adult rheumatology population and highlights the emerging role of TGF-β inhibition in halting disease in a range of inherited connective tissue disorders linked by a common pathogenic pathway.

**Rheumatology key message**

- LDS should be considered in adult hypermobility and management involves angiotensin II antagonism and surgery.

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

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**References**


**Anti-TNF-α therapy prevents the recurrence of joint bleeding in haemophilia and arthritis**

Sir, Haemophilia A is a deficiency or functional defect of coagulation factor VIII, resulting in severe bleeding episodes during life [1, 2]. Haemophilic arthropathy (HA) is caused by recurrent joint bleeding and, if untreated, leads to severe chronic arthropathy characterized by pain and permanent functional disability [3]. In HA, synovitis and arthritis secondary to chronic joint bleeding are well-known complications [4, 5]. We describe the case of a 51-year-old patient with severe haemophilia A with HBV [HBV DNA <20 IU/ml, anti-haemoglobin C (Hbc) positive]/HCV (HCV RNA 348 000 IU/ml, genotype 1a). The onset of pain and swelling of all metacarpophalangeal and interphalangeal joints, positive RF and CCP antibodies (CCP-a) and an increase in ESR and CRP (DAS 28:5:2) prompted the diagnosis of RA. Joint ultrasonography showed synovitis and joint effusion of the wrists and metacarpophalangeal joints with power Doppler activity [6]. In 2005, due to worsening of the disease (DAS 28:5:8), adalimumab (40 mg s.c. every other week) was prescribed. A QuantiFERON test (QFT) and purified protein derivative (PPD) test were negative. The treatment with adalimumab together with low steroid doses, HCQ
(200 mg/day) and lamivudine (100 mg/day) led to disease remission (DAS 28:2) with no power Doppler joint activity on US and no haemarthroses. A second case was a 26-year-old male patient affected by haemophilia A, psoriasis and long-standing HA of the left ankle and elbow. In 2007 PsA was diagnosed after he presented with pain and swelling of all metacarpophalangeal and interphalangeal joints (RF and CCP-a negative, Cw06, B51) with increased ESR and CRP (DAS 28:<2.6). US showed no effusion and power Doppler (PD) activity. The patient is still on MTX and adalimumab and has not experienced any joint bleeding.

A third case was a 49-year-old male patient affected by haemophilia A, psoriasis, HIV (HIV RNA 1500 IU/ml) and HCV (HCV RNA 899 000 IU/ml, genotype 2a) on highly active antiretroviral therapy (HAART) to control an HIV infection since 1996. Since 2007 he has been treated with IFN-α and ribavirine to suppress his HCV load. In January 2009, after 1 year of recurrent joint bleeding, he presented with swelling and pain of the proximal interphalangeal joints, ankles and metatarsal joints. ESR and CRP were increased (DAS 28:3.6). US showed synovial effusion of both ankles and feet and the metacarpophalangeal joints and PD activity. Psoriasis was evident and PsA (B27 positive) was diagnosed. PPD and QFT results were positive and PD activity. HIV RNA was negative and HCV RNA was <15 IU/ml.

Before treatment with recombinant factor VIII (FVIII) concentrate, in all patients the recurrent joint bleedings were >10 per year. Since 2000, two patients on secondary prophylaxis with FVIII (30 IU/kg three times per week) have obtained a reduction in joint bleeding (Fig. 1). The third patient was treated on demand with FVIII (40 IU/kg) every time he had joint bleeding without any change in the number of bleeding episodes. The treatment was approved by the local ethical committee (Ethics Committee Azienda Ospedaliero Universitaria Careggi) and each patient signed an informed consent according to the Declaration of Helsinki.

These HA cases, with overlapping RA or PsA, as a preliminary study, demonstrate that anti-TNF-α not only controls disease remission, but also may lead to a significant reduction in joint bleeding. One of the major problems was the concomitant viral infections (HIV, HCV, HBV) that are usually a major contraindication to anti-TNF-α treatment [7, 8]. The infectious and hematological screening performed in each patient before starting adalimumab and the serological monitoring (every 3 months) were very important to prevent the onset of complications. As regards HCV infection, TNF-α may play a role in controlling liver damage and therefore treatment with anti-TNF-α could have had a therapeutic effect [9]. It is well known that HBV infection may be reactivated by anti-TNF-α therapy and for this reason the treatment with lamivudine was started. The risk of underlying HBV reactivation may occur only after withdrawal of immunosuppression (immune reconstitution) [10], and since occult HBV infection cannot be eliminated, careful follow-up is necessary during and after treatment. In conclusion, anti-TNF-α therapy may be safely used in haemophilia A associated with chronic arthritis, even when viral infections are present. Careful follow-up of these patients with complex clinical features is mandatory.

**Rheumatology key message**

- The anti-TNF-α therapy in haemophilic arthropathy patients induces a decrease in both synovitis and haemarthroses.

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**References**

Comment on: The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis

Sir, Matcham et al. [1] recently reported a meta-analysis on the prevalence of depression in RA. Among several definitions of depression, the authors selected four definitions from three methods for calculating pooled estimates of the prevalence of depression. They concluded that depression was prevalent in RA patients, although the prevalence differed according to the diagnostic procedure. In addition, the authors concluded that prevalence decreased with age by using ecological data. I have some concerns about the study outcome.

First, the authors used a quality assessment tool to classify the quality of each study. The number of studies with a quality assessment score ≥ 7 was 3 out of 32 studies and the number of studies with a quality assessment score of 0 was 6 out of 32 studies. As a trend, structured clinical interviews according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) were handled with relatively high-quality assessment scores, but the authors could not systematically consider it for their meta-analysis.

Second, the authors referenced two papers by the same authors with different dates of publication [2, 3]. The prevalence of depression judged by different cut-off points of the Hospital Anxiety and Depression Scale (HADS) was 20%, which should be clarified with special reference to the characteristics of the target patients.

Third, there are several factors affecting the prevalence of depression in RA patients, such as pain and a decrease in the quality of life due to disease progression. Meta-analysis by compiling studies should be handled with caution, although mathematical procedures can be applied. With reference to fig. 2 in Matcham et al., HADS with a threshold of eight and the Centre for Epidemiologic Studies Depression Scale need cause analysis before meta-analysis, because each study showed a wide range in the prevalence of depression.

The authors checked publication bias and the effect of seven factors on prevalence estimates. As there is a limitation in ecological data to determine related factors in the prevalence of depression [4], further studies are required.

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Comment on: The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis: reply

Sir, We thank Tomoyuki Kawada for his letter about our article [1]. We agree that our systematic review indicated that a high proportion of studies in this area were of suboptimal quality and also that interpretation has to be tempered by taking account of the diversity of measures used and the methodological quality [2]. While we accept these are limitations of the primary studies, there is little we as reviewers can do, other than conduct sensitivity analyses and make...