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Ankylosing Spondylitis: Update on Imaging and Therapy

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Research in the field of ankylosing spondylitis (AS) and related spondyloarthropathies has gained increasing interest in recent years. Magnetic resonance (MR) imaging and the introduction of highly effective tumor necrosis factor-α (TNF-α) inhibitors represent major recent advances. MR imaging is emerging as a useful tool to facilitate early diagnosis of AS. Recent progress in MR technology with the advent of whole body MR imaging has expanded the imaging modalities in the field of AS. TNF-α inhibitors are proven to be highly effective in suppressing disease activity and improving functional ability and quality of life of patients with AS. Future research activities will focus on tools for an early diagnosis and on testing the hypothesis that TNF-α inhibitors may retard the progression of spinal structural damage. Int J Adv Rheumatol 2007;5(1):2–7.

Ankylosing spondylitis (AS) is a chronic systemic inflammatory rheumatic disorder of uncertain etiology that primarily affects the axial skeleton; sacroiliac (SI) joint involvement (sacroilitis) is one of its hallmarks [1]. It belongs to a group of rheumatic diseases known as the spondyloarthropathies [2]. Symptoms usually start in the late teens and early twenties with chronic inflammatory back pain, but clinical manifestations vary. The disease can lead to progressive limitation of spinal mobility and result in physical impairment and adverse socioeconomic consequences [3–5].

Delayed diagnosis

Diagnosing AS at an early stage is not a simple task: there are no established criteria for its early diagnosis, and many patients may have atypical presentations [6,7]. Although some patients do not seek help early in the course of their disease, many do. However, their symptoms are not recognized for a variety of reasons, and multiple referrals of such patients to different specialists for their various complaints often do not result in a correct diagnosis for many years [1–3,6–8].

The modified New York criteria designed for AS disease classification are often used for diagnostic purposes [9]; however, they depend on the presence of sacroilitis on standard radiographs, which generally appears late in the disease course. In a cohort of 88 patients with clinically suspected early AS, radiographical sacroilitis became evident only after a mean disease duration of 9 years [10]. However, recent advances in musculoskeletal imaging, especially magnetic resonance (MR) imaging, can be used to help diagnose the disease at an earlier stage when pelvic radiographs do not show sacroilitis. In recent years, MR imaging has become the preferred imaging method for detection of early inflammation of the SI joints and the spine in AS [11–16].

MR imaging in the assessment of AS

MR imaging sequences

T2-weighted, fat-suppressed MR sequences and Short Tau Inversion Recovery (STIR) MR sequences represent the most important techniques for detecting active inflammatory lesions and assessing disease activity in AS. T1-weighted spin echo sequences may be used to visualize bony sclerosis and erosions, as well as syndesmophyte formations. The quality of information gained by the STIR technique alone in imaging spinal inflammatory lesions in AS is not inferior to that provided by gadolinium-enhanced T1-weighted imaging with fat suppression [17]. In daily practice, gadolinium-enhanced sequences (and their associated cost) do not add significant information compared with STIR as the sole imaging technique.
What is the clinical relevance of signal alterations in MR imaging?

Whether the bone marrow signal abnormalities that are seen on MR imaging of AS represent a specific inflammatory feature has not been clarified [18]. Ill-defined signal alterations seen on fluid-sensitive sequences such as those comprising STIR images or T2-weighted, fat-suppressed images are commonly considered to represent “bone marrow edema”. However, this term is misleading since marrow edema is rarely found upon histological examination [19]. In a recent study in rheumatoid arthritis, the so-called “bone marrow edema” corresponded histologically to inflammatory infiltrates invading the bone marrow [20]. A correlation between clinical disease activity and active inflammatory changes of the SI joints and the spine in AS has been found in some studies [21,22], while there have been negative findings in others [23,24].

Where are the most common locations of inflammatory lesions in the axial skeleton found by MR imaging?

Early signs of inflammation in MR imaging studies in AS have been consistently found in the inferior iliac quadrant of the SI joints (Figs. 1A, 1B, and 1C) [25,26]. A recent study with MR–histology correlation of normal SI joints confirmed that the synovial part of this joint is confined to the inferior (distal) cartilaginous portion at the iliac side [27]. It is not yet known if fatty replacement of subchondral bone marrow close to the SI joints represents a distinct feature in AS [28]; they have been reported to be frequently associated with chronic inflammatory changes of these joints in a study of 41 patients with early spondyloarthritis [11]. On the other hand, fat conversion of a mostly patchy distribution has been described in the sacral and iliac bone marrow in some healthy volunteers without known inflammatory disease [14,29,30].

Inflammatory changes in the lower thoracic spine on MR imaging seem to be second in frequency only to inflammatory lesions in the SI joints [21,23,31]. This finding may contribute to early diagnosis of AS; therefore, in an ideal situation, the lower thoracic spine should be part of MR imaging protocols in AS [31]. A high frequency of inflammatory lesions not only in the vertebral bodies, but also in the posterior structures of the spine, especially in the thoracic segment, was found in a recent systematic MR evaluation; these lesions were responsive to treatment with tumor necrosis factor-α (TNF-α) antagonists [32]. Supplementary sagittal slices that extend to the lateral edges of the vertebrae need to be added to standard MR protocols of the thoracic spine to visualize inflammatory lesions in the costovertebral and costotransverse joints, as well as the facet joints (posterior elements) [33].

Inflammatory involvement of the lumbar spine without major changes in the SI joints has been seen occasionally [34].

What is the place of MR imaging in the diagnosis of suspected AS?

MR imaging is part of the Assessment in Ankylosing Spondylitis (ASAS) International Working Group recommendations for management of AS [35]. As a collaboration between ASAS...
and the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) initiative, an MR imaging in AS working group has started with the goal of validating and standardizing the available MR scoring systems for the spine and the SI joints [18]. A multireader experiment investigating three scoring methods of spinal MR imaging lesions showed a comparable ability of these methods to assess change in disease activity [36].

Rudwaleit et al. have reviewed published studies and summarized the reported specificity, sensitivity, and likelihood ratio (LR) for the various clinical features, laboratory findings, and skeletal imaging techniques that clinicians rely on to diagnose AS [37]. A subsequent study also reported that the sensitivity of MR imaging for detection of active inflammatory lesions of the SI joints in two cohorts of patients with suspected early AS (with the judgement of the treating rheumatologist serving as the gold standard) ranged from 67% to 85%, and the specificity was 91% (since only 9% of controls [individuals who had mechanical lower back pain] showed such lesions) [38]. Diagnostic algorithms have also been published to help clinicians in diagnosing AS in an early (pre-radiographical) stage [39,40].

**What is the role of MR imaging in assessing disease activity and monitoring treatment?**

In daily practice, MR imaging is increasingly being used as an additional tool to assess disease activity in suspected early AS. There are no data on whether widespread inflammatory lesions in the axial skeleton are indicative of a poor prognosis, and additional data are needed to test if acute (active) inflammatory lesions seen on MR imaging are indeed predictive of future radiographical structural damage [13]. This question is highly relevant since clinical trials with TNF-α inhibitors demonstrate a regression of active inflammatory lesions in the axial skeleton, fuelling the hope for delaying disease progression and improving long-term prognosis.

In clinical studies, a good correlation between suppressing clinical disease activity and active inflammatory lesions of the axial skeleton found by MR imaging has been shown for all of the three anti-TNF-α agents (adalimumab, etanercept, and infliximab), after a treatment duration of 12–52 weeks [41–44].

**Whole body MR imaging: a recently introduced modification**

Recent advances in MR methods such as multichannel technology and parallel imaging make it possible to perform whole body MR imaging with visualization of inflammatory lesions in the entire spine and the SI joints, as well as in the shoulders, the anterior chest wall, and the pelvis (Figs. 2–4). It takes only 30 min or less to perform, including the initial positioning of the patient [45]; novel matrix coils reduce imaging time by virtually eliminating the need for patient repositioning and manual coil changes. Spatial resolution is similar to that of standard MR examinations. In terms of reporting time, it takes a trained reader approximately 15 min.

Inflammatory lesions of the shoulders, the anterior chest wall, and the pelvis found by MR imaging have not been extensively investigated in AS [15,46]. There is some evidence, however, that inflammation of the hip joint may signify a poor prognosis with respect to spinal fusion [47,48]. Whole body MR imaging can be used to visualize inflammatory changes in the hip joints simultaneously to those in the SI joints and the entire spine. Inflammatory involvement of the anterior chest wall in MR examinations has rarely been reported in AS [15]. In contrast, inflammatory involvement with intense bone
marrow abnormality at the supraspinatus insertion onto the greater tuberosity and acromial entheses of the deltoid muscle has previously been described in AS [46].

A systematic comparison of the quality of information gained by whole body MR imaging and by the assessment of selected regions of the skeleton using conventional MR imaging techniques is a current research topic.

**Management**

The management of a patient with AS should be individualized based on the symptoms and signs, the disease activity and severity, functional status, deformities, general health status, comorbid conditions, and the patient’s wishes [49–52]. For a chronic disease such as AS, the goal of treatment should be not only relieving the clinical symptoms, but also halting or slowing the disease progression, and maintaining good posture and good physical and psychosocial functioning.

The long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with non-pharmacological modalities (exercise and physical therapy) has been the mainstay of therapy for more than five decades, and it is effective in controlling pain and stiffness, and in maintaining mobility in a sizeable proportion of patients [49–51]. Both traditional NSAIDs and selective cyclooxygenase 2 inhibitors have been shown to decrease axial and peripheral joint pain and improve function in patients; they need to be taken regularly in full anti-inflammatory doses to achieve the desired therapeutic effect. But there is as yet no cure for AS, and management can be quite a challenge for patients with severe disease or those who cannot take NSAIDs.

**Therapeutic options**

It is rare that a truly novel and revolutionary therapy becomes available, particularly for diseases in which few treatments are effective. This phenomenon has finally become a reality for patients with AS, with the advent of therapy with TNF-α inhibitors [3]. All three TNF-α inhibitors (adalimumab, etanercept, and infliximab) have been shown to be remarkably effective in AS – more so than in rheumatoid arthritis – without the need for concomitant therapy with conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX) [3,35,53–59]. At present, based on benefit–risk ratios, there is a consensus among rheumatologists interested in AS that at this stage only patients with AS who have severe disease that cannot be well controlled with conventional treatment (i.e. their BASDAI [Bath Ankylosing Spondylitis Disease Activity Index] score is ≥4 on a scale of 0–10 [10 being the worst]) should be treated with TNF-α inhibitors [35].
Early identification of variables that help to predict severe disease with a poor functional prognosis is now needed. If biological therapy with TNF-α inhibitors is proven to retard disease progression and prevent or delay functional limitations, insight into such prognostic tools will help clinicians to offer the correct treatment to the correct patient at the correct time [3]. There is also a need to demonstrate long-term benefits of the therapy, as well as a favorable cost–benefit ratio, to help to convince healthcare authorities, insurance companies, and others of the utility of these drugs for treating patients with AS that is refractory to conventional drug therapy [3].

ASAS and the European League Against Rheumatism (EULAR) have recently published the first international recommendations for the management of AS [35]. The recommendations contain 10 key components that provide practice guidance for appropriate monitoring and treatment of patients, with the ultimate objective of contributing to better outcomes for these individuals. The ASAS/EULAR expert opinion was based on scientific evidence for efficacy, safety, and cost-effectiveness, and on the clinical expertise of the clinicians involved (covering logistics, patient-perceived acceptance, and tolerability). Below are some of the highlights of these recommendations:

- Long-term use of NSAIDs, patient education, and a lifelong program of appropriate physical exercises still form the first step in the management of AS [35].
- Patient education and counseling, including self-help programs, improve patients’ compliance with therapeutic regimens, decrease their pain, and may have a positive impact on general health status [35, 52].
- Individual and group physical therapy, patient associations, and self-help groups may be useful [35].
- The available evidence does not support the use of systemic corticosteroids for the treatment of axial disease in AS [35].
- The traditional DMARDs, including MTX, leflunomide, and sulfasalazine, are not indicated for the treatment of axial disease, whereas TNF-α blockers are remarkably effective in treating patients with AS who have a persistently high disease activity and a lack of response to conventional therapy with NSAIDs [3, 35]. Therefore, there is no need for obligatory use of DMARDs prior to or concomitant with anti-TNF-α therapy for patients with AS [35].
- Total hip arthroplasty should be considered in patients with refractory hip pain or disability and radiographical evidence of severe structural damage [35].
- Spinal surgery, such as corrective spinal osteotomy for severe kyphotic deformity and spinal fusion procedures for segmental instability or fracture, may be indicated in selected patients [35].

**Conclusion**

The patient’s symptoms, family history, and articular and extra-articular physical findings offer the best clues in diagnosing AS, while radiographical evidence of sacroiliitis provides the best non-clinical indicator of the presence of disease. However, the status of SI joints in routine pelvic radiographs may not always be easy to interpret in the early phase of the disease. MR imaging is emerging as a reliable diagnostic tool in patients with suspected early AS, but further data are needed before the radiographical criterion of sacroiliitis can be replaced by MR imaging findings for early diagnosis of AS. Whole body MR imaging is a promising technique to assess acute inflammatory lesions in the entire axial skeleton, and the shoulder and pelvic girdles.

The ASAS/EULAR recommendations for the management of AS have recently been published [35]. The optimal management of AS requires a combination of non-pharmacological and pharmacological treatments. A lifelong exercise program and long-term regular use of NSAIDs provide the cornerstone of treatment for AS; however, the traditional DMARDs, including MTX, leflunomide, and sulfasalazine, are not recommended for the treatment of axial disease.

Early diagnosis is crucial now that more effective therapy is available in the form of anti-TNF-α agents – adalimumab, etanercept, and infliximab. All three are remarkably effective in suppressing disease activity and improving the functional ability of patients with AS whose disease is refractory to conventional therapy. Functional disability is the most important predictor of high total costs; therapeutic interventions that improve a patient’s functional ability should appreciably reduce the overall socioeconomic burden of diseases such as rheumatoid arthritis and AS [60].

**Acknowledgement**

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**Disclosures**

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**References**


Current knowledge on Behçet's syndrome (BS) perhaps involves more about what it is not than what it is. This multisystem disorder is certainly not a typical autoimmune disease, as there is no definite heightened B cell function or impaired T cell activity [1,2]. In addition, there is no female dominance like that commonly found in classic autoimmune disorders. In fact, there are approximately equal prevalences among the two sexes, although a more severe course is observed among males [3]. The clinical findings, especially the distinctive cutaneous and mucosal lesions, are quite different from those of other autoimmune disorders. In fact, there are approximately equal prevalences among the two sexes, although a more severe course is observed among males [3]. The clinical findings, especially the distinctive cutaneous and mucosal lesions, are quite different from those of other autoimmune disorders, and there is little association with Sjögren's syndrome [4].

The fact that the clinical activity usually abates with the passage of time, with no major increase in propensity to atherosclerosis, is another important differentiating aspect [3,5,6]. While there is evidence for a genetic predisposition [7,8], there is no well-defined pattern of inheritance. The most consistently reported association – that with human leukocyte antigen B51 (HLA-B51) – fails to completely account for the familial risk observed among siblings [9]. Although previous attempts to classify BS with the spondyloarthropathies have been unsuccessful [10,11], it has been recently reported that a subgroup of patients with BS might show some features of reactive arthritis and enthesopathy [12]. Finally, problems with classifying BS have also been noted with regard to current understanding of autoinflammatory diseases [13]. Autoinflammatory conditions typically involve a well-defined pattern of genetic markers, juvenile onset, periodic serositis, febrile attacks, and a lifelong non-abating course (unless treated); these are not usually characteristics of BS [14].

How is BS described?

BS is characterized by recurrent mucocutaneous lesions and sight-threatening ocular involvement [15]. It also affects joints, vessels of all types and sizes, the central nervous system (CNS), and the gastrointestinal system. It is seen mainly in the Mediterranean basin, the Middle East, and the Far East. Turkey has the highest prevalence: 8–42 cases per 10 000 people [15]. The frequency is much lower in Western countries: 0.07–3 cases per 10 000 people [15]. As mentioned above, there are approximately equal prevalences among the two sexes; however, the majority of female patients complain of only mucocutaneous lesions, while most males are subject to at least one major organ involvement, which is typically ocular, vascular, or neurological in nature [3]. The mean age of onset is in the third decade, although the disease appears rarely in childhood (2.2%) or among people aged >50 years (1.7%) [15]. There is a relapsing clinical course; the frequency
and the severity of the relapses usually diminishes with time. However, BS can cause substantial morbidity, such as blindness and debility, and can lead to an increased mortality rate. Recently, it has also been shown that BS leads to a considerable economic burden for the healthcare services in an endemic region [16].

**How can BS be diagnosed?**

There are no specific laboratory tests for BS; the diagnosis is mainly clinical. The International Study Group (ISG) diagnostic criteria, developed in 1990, are the criteria most commonly used for disease classification [17]. Oral ulceration is a *sine qua non* of BS, but diagnosis require at least two other criteria to be satisfied (Table 1). The original evaluation of the criteria, which had included patients with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and psoriatic arthropathy as the control group, had found the sensitivity and specificity values to be high (both >90%) [17]. Another study reassessed the ISG criteria, this time including controls with inflammatory bowel disease and familial Mediterranean fever [18]. The performance of the criteria was again found to be robust.

**What are the clinical manifestations of BS?**

A summary of the clinical manifestations of BS – which are discussed in more detail below – is provided in Table 2.

**Mucocutaneous lesions**

**Oral ulcers**

Oral ulcers (Fig. 1) are the most prevalent lesions in BS and can exist for many years before other manifestations occur. These ulcers are similar to idiopathic recurrent aphthous stomatitis, in terms of discomfort, appearance, localization, and histopathology. They are mostly found on the gums, tongue, and mucosal portions of the lips and cheeks. Only rarely is the posterior part of the pharynx affected. In contrast to herpetic sores, they do not affect the outer portions of the lips.

**Genital ulcers**

Genital ulcers (Fig. 2) look like punched-out lesions and they have the same histology as oral ulcers [15]. However, they are deeper, larger, and less prevalent than oral ulcers. The

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**Table 1. International Study Group criteria for the diagnosis of Behçet’s syndrome [17].**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tr>
<td>The patient must have</td>
<td>Aphthous or herpetiform lesions; observed by the physician or patient; recurring ≥3 times per year</td>
</tr>
<tr>
<td>Recurrent oral ulceration</td>
<td>Aphthous ulceration or scarring observed by the physician or reliably described by the patient</td>
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<tr>
<td>Recurrent genital ulceration</td>
<td>Anterior or posterior uveitis, cells in the vitreous body on slit-lamp examination, or retinal vasculitis detected by an ophthalmologist</td>
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<tr>
<td>Ocular lesions</td>
<td>Erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules, not related to glucocorticoid treatment or adolescence</td>
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<tr>
<td>Skin lesions</td>
<td>Test results interpreted as positive by the physician at 24–48 h</td>
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**Table 2. Clinical manifestations of Behçet’s syndrome.**

<table>
<thead>
<tr>
<th>Mucocutaneous lesions</th>
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<tr>
<td>Oral ulcers</td>
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<tr>
<td>Genital ulcers</td>
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<tr>
<td>Papulopustular lesions</td>
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<tr>
<td>Erythema nodosum</td>
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<th>Joint lesions</th>
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<td>Arthralgia</td>
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<td>Mono- or oligoarthritis</td>
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<th>Eye involvement</th>
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<td>Anterior uveitis</td>
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<td>Posterior uveitis or panuveitis</td>
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<td>Retinal vasculitis</td>
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<tr>
<th>Vascular lesions</th>
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<tr>
<td>Venous type</td>
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<tr>
<td>Superficial thrombophlebitis of the extremities</td>
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<td>Deep vein thrombosis of the extremities</td>
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<tr>
<td>Large vein thrombosis (affecting the vena iliaca or vena cava, for instance)</td>
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<tr>
<td>Arterial type</td>
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<tr>
<td>Arterial aneurysms</td>
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<tr>
<td>Arterial thrombosis or occlusions</td>
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<tr>
<th>Neurological involvement</th>
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<td>Dural sinus thrombosis</td>
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<td>Parenchymal involvement</td>
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<td>Aseptic meningitis</td>
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<td>Intracranial hypertension</td>
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Ulcers are usually painful, and they heal in 10–30 days, frequently leaving scars [19]. They can be complicated with secondary infection, especially among females. Genital ulcers commonly occur on the scrotum in males and on the labia majora and the labia minora in females. Ulcers healing with scars are helpful in the clinical diagnosis of BS, as such lesions are not usually found in other connective tissue diseases or vasculitides. In contrast to herpes simplex and reactive arthritis, the glans penis is rarely affected and urethral discharge or dysuria seldom occurs. Similarly, the cervix and vagina, which are common sites for herpes simplex manifestations in females, are rarely affected in BS.

Acne and papulopustular lesions
Acne and papulopustular lesions (Fig. 3) are found in approximately 85% of patients with BS and are usually located on the face, neck, shoulders, upper chest, buttocks, and femoral regions [15]. Among patients with BS, papulopustular lesions are seen more often in those who have arthritis [20]. It is difficult to differentiate the acne-like lesions of BS from acne vulgaris, either clinically or histologically. In contrast to what is seen in acne vulgaris, however, acne-like lesions found in BS can be located on the upper and lower extremities. The bacteriological examination is also somewhat different. *Staphylococcus aureus* and *Prevotella* spp. have been found to occur significantly more often in the pustules of patients with BS than those of patients with ordinary acne [21].

Nodular lesions
There are two main types of nodular lesions in BS: erythema nodosum (EN; Fig. 4) and superficial thrombophlebitis (STP). These two types of lesions can be indistinguishable from each other with the naked eye. EN lesions are more common in females, while STP lesions are more common among males and are associated with large vessel involvement [15]. On closer examination, manifestations of STP are seen as string-like lesions following vein tracts. Both B-mode and Doppler ultrasonography can be helpful in differentiating between the two types of nodular lesions [22].

EN lesions associated with BS may leave brown pigmentation on healing and sometimes ulcerate, distinguishing them from those associated with other conditions. In addition, the lesions associated with BS are less well demarcated. Histopathological examination of these lesions shows not only septic panniculitis (as observed in idiopathic EN), but also medium vessel vasculitis in approximately half of the cases [23]. STP lesions involve large and small veins of the lower extremities, the great saphenous vein being most commonly affected. Histological examination reveals organized thrombi in the lumens of involved veins.

The pathergy test
A pathergy reaction (an exaggerated non-specific inflammatory response to a minor trauma) occurs in approximately 60% of patients [15]. The frequency of a positive test result (formation of a papule or pustule 24–48 h after a sterile dermal pinprick; Fig. 5) is higher among the countries where BS is most prevalent [24]. This diagnostic tool is highly specific but less sensitive. Male patients and those with active disease have stronger reactions [25]. Pathergy reaction is almost unique to BS. Pyoderma gangrenosum and Sweet’s syndrome are among the few other conditions in which it occurs.

Arthritis
Joint disease in the form of monoarthritis or oligoarthritis is seen in approximately 30–50% of patients with BS [26]. The knees, ankles, wrists, and elbows are frequently affected, and the episodes are usually self-limited, resolving in 2–4 weeks without causing deformity or erosion on radiography.

There is a debate concerning whether BS could be a part of the spondyloarthropathy complex, since there are some shared clinical features and some case reports showing their coexistence [11]. The usual sparing of the sacroiliac joint, the lack of spinal involvement, the absence of an HLA-B27 association, and the difference in the clinical spectrum of ocular involvement (potentially blinding, severe panuveitis – rather than anterior uveitis or conjunctivitis – is seen in BS)
argue against this hypothesis [10,11]. However, it has been reported that patients with BS and arthritis are more prone to have papulopustular lesions than those with BS only [20], as mentioned earlier. An isolated cluster has also recently been proposed in BS, which bears reactive arthritis-like features such as acne, arthritis, and enthesitis [12].

Ocular disease
Ocular involvement is the most serious manifestation of BS and is seen in approximately 50% of cases [15]. It develops within the first few years of disease onset, the time when it runs its most severe course; new ocular involvement is rare after 4–5 years of the disease course have passed [3]. The ocular pathology in BS can be defined as a combination of recurrent attacks of non-granulomatous uveitis and retinal vasculitis. This can lead to cataracts, glaucoma, and eventually phthisis bulbi. Conjunctivitis, scleritis, and episcleritis are rare in BS; furthermore, there is an absence of sicca symptoms [15]. Isolated anterior uveitis is present in approximately 10% of cases of ocular involvement and has a relatively favorable prognosis [27,28]. Posterior uveitis or panuveitis associated with retinal vasculitis is found in approximately 90% of cases of ocular involvement and presents a management challenge since the lesions affecting the posterior segment have a persistent nature and are correlated with significant loss of vision [29]. This kind of involvement needs to be treated vigorously. Hypopyon (Fig. 6) is observed in 10% of cases of ocular involvement and has the onset of ocular disease [31]. More recent studies, especially those done after 1990, report a better outcome, probably owing to early and aggressive treatment [32]. However, even with treatment, the progression of ocular disease cannot always be prevented [3,27]. In one large, prospective cohort study, loss of useful vision was present at first visit in 17% of males and 10% of females [3]. At the end of 20 years, an additional 27% of males and 11% of females had lost their useful vision. In another large follow-up study, loss of useful vision at 10 years was predicted to be 30% and 17% for males and females, respectively under conventional immunosuppressive treatment [27].

Vascular involvement
BS is one of the few vasculitides that can involve both the venous system and the arterial system, and there is a definite male preponderance. Venous involvement is more common than arterial disease, being observed in 75% of all cases with vascular involvement [3,15].

Venous involvement
Deep vein thrombosis (DVT) is the most common type of venous involvement (occurring in 80% of cases); it is mainly localized in the lower extremities but may manifest at other sites such as the superior vena cava and upper extremity veins. It is also one of the early manifestations of BS, usually occurring in the first few years after disease onset. Acute venous thrombosis of the lower extremities causes pain, erythema, and swelling. Recurrent attacks of venous thrombosis may lead to chronic venous insufficiency and post-thrombophlebitic syndrome, which can be manifested by varices, hyperpigmentation, skin thickening, and ulcers (Fig. 7). DVT may extend to large vessels such as the iliac and hepatic veins or to the inferior vena cava. It has been shown that STP and DVT may occur in conjunction with each other [33,34]. Furthermore, DVT has been found to be associated with dural sinus thrombi (DST; described in more detail later) [35]. The association between STP, DVT, and DST represents a potential
“vascular cluster”, adding to the reactive arthritis-like cluster described above. The apparent presence of these clusters in patients with BS suggests that several different factors may play a role in the pathogenesis.

Among all types of venous involvement, Budd–Chiari syndrome has the most associated outcome, with a mean survival period of 10 months and a mortality rate of 60–100% [3,36]. As a rule, embolic phenomena are rare in vascular disease in BS. This could be attributable to tight adherence of the thrombus to the vessel wall, as revealed in post mortem examinations [15]. Therefore, the role of anticoagulation in venous disease is debatable.

Arterial involvement

Arterial involvement is characterized by thrombotic occlusion or aneurysm formation [3,15]; it usually develops later during the disease course, has a more acute onset, and is more life threatening than venous disease. Typical involvement sites are the pulmonary arteries, the abdominal aorta, and the iliac, femoral, popliteal, and carotid arteries. Intracardiac thrombus is also a part of the clinical spectrum. Involvement of the renal, cerebral, and coronary arteries has been reported rarely [15]. Each form of arterial lesion frequently coexists with venous thrombosis. Ischemic pain distal to the involvement site, absence or reduction of the pulse, bruises, and pulsatile mass are the typical clinical features of abdominal and peripheral arterial involvement. Pulmonary artery aneurysms are emerging as a life-threatening complication of BS, with rupture resulting in massive hemoptysis [37]. They are largely confined to the main pulmonary arteries and their lobar branches, and they appear as nodular hilar mass lesions on X-ray that can be indistinguishable from the lesions of a lymphoma, tuberculosis, or fungal infection [38].

Neurological involvement

There are two main types of neurological disease in BS: parenchymal CNS disease, which is the most common (occurring in 75–80% of cases of neurological involvement); and DST (which occurs in 10–20% of cases) [39,40]. Aseptic meningitis and arterial involvement are rare types (1–2% of cases). The frequency of all types of neurological involvement among patients with BS is reported to be approximately 5–6% in cross-sectional studies [39,40]. However, this rate can double in cohorts that are followed in the long term [3].

Parenchymal CNS disease

Parenchymal CNS disease is a late manifestation of BS, developing 5–10 years after disease onset. Brainstem involvement is the most characteristic type of manifestation [39,40]. Spinal cord and hemispheric involvement are rarely observed. Furthermore, peripheral neuropathy is rare, as is mononeuritis multiplex. Pyramidal signs, hemiparesis, behavioral–cognitive changes, sphincter disturbances, and impotence are the main clinical manifestations. Cerebrospinal fluid changes are non-specific for neurological disease in BS; mild protein elevation and mild-to-moderate lymphocytic pleocytosis are generally observed. Neuroimaging examinations, especially with magnetic resonance imaging, can be helpful to detect large brainstem lesions with indistinct borders. These lesions may occasionally show extensions into the diencephalon and basal ganglia. Isolated hemispheric lesions and hemorrhagic venous or arterial infarcts are not observed. The disease may follow a relapsing–remitting course and will progress to severe disability in 50% of cases over 10 years [40]. In a long-term mortality survey, parenchymal neurological disease was identified as the second most common cause of mortality in BS [3].

DST

DST is an early finding in the disease course. It is associated with a relatively favorable outcome and is usually seen in conjunction with other types of venous disease [39,40]. Thrombosis of the venous sinuses may present with symptoms of increased intracranial pressure, such as severe headache, papilledema, and sixth nerve palsy, and rarely with fever; the superior sagittal sinus is the site most commonly affected.

Conclusion

BS is still defined mainly clinically, but there are an array of distinguishing features that can help in differentiating it from connective tissue diseases and other systemic vasculitides. The newly proposed clinical clusters – one comprising acne, arthritis, and enthesopathy, and the other comprising STP, DVT, and DST – may help in diagnosis and management, and perhaps also in elucidating the pathogenesis.

Disclosure

The authors have no relevant financial interests to declare.

References

Safety of Biological Agents in Patients with Active Rheumatoid Arthritis

Calin Popa and Piet LCM van Riel

Therapeutic strategies that interfere with pro-inflammatory cytokines have represented a breakthrough in the treatment of rheumatoid arthritis and other inflammatory disorders over the last decade. However, key safety issues related to the use of these drugs, particularly tumor necrosis factor-α (TNF-α) blockers, have been reported. Infections represent the most frequently reported side effect of TNF-α blockade. Among them, those involving Mycobacterium tuberculosis are some of the most severe. Multiple mechanisms responsible for this side effect have been proposed, including an inhibition of interferon-γ production and leukocyte apoptosis. Currently, screening for latent tuberculosis infection is recommended before starting therapy with adalimumab or infliximab and is prudent with etanercept use; caution must be applied when these treatments are given to patients who are at increased risk of infections. In addition to infections, especially those involving M tuberculosis, this review covers a number of other side effects associated with TNF-α blockade, including heart failure, lupus-like syndrome, demyelinating disorders, and malignancies. Int J Adv Rheumatol 2007;5(1):14–8.

Infections

TNF-α is a pleiotropic cytokine and its role in inflammatory processes is complex. It stimulates the production of other pro-inflammatory cytokines including IL-1β, IL-6, and interferon-γ and participates in the recruitment and activation of other immune cells at the site of the inflammatory process by stimulating the expression of adhesion molecules and the maturation of inflammatory cells [4,5]. Moreover, TNF-α is involved in the killing of invading microorganisms, particularly intracellular microorganisms, by promoting the release of proteolytic enzymes and contributing to the formation and maintenance of granuloma [6]. Therefore, it is not unexpected that a number of serious infections have been confirmed with the therapeutic blockade of this cytokine. Cases of fungal infections and opportunistic infections including tuberculosis (TB), pneumocystosis, histoplasmosis, aspergillosis, listeriosis, and salmonellosis have been reported during the use of anti-TNF-α agents [7–11]; TB is described below.
TNF-α

Mechanisms of action

Of the three anti-TNF-α agents that are currently on the market, two of them are monoclonal antibodies: adalimumab is a fully humanized monoclonal antibody and infliximab is a chimeric monoclonal antibody. The other agent, etanercept, is a soluble TNF-α receptor also known as TNFRp75. While all of these agents are directed to bind and therefore block TNF-α, many differences between them have been reported.

Therapeutic spectrum and effectiveness of the main TNF-α-blocking agents currently marketed.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
</tr>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>++* [38]</td>
<td>+++ [42]</td>
<td>+++* [49]</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>++* [39]</td>
<td>++* [43]</td>
<td>+* [50]</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>+ [40]</td>
<td>-* [44]</td>
<td>++* [51]</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>+* [41]</td>
<td>++* [45]</td>
<td>++* [52]</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>NA</td>
<td>+* [46]</td>
<td>+ [53]</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>NA</td>
<td>– [47]</td>
<td>+ [54]</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>NA</td>
<td>–* [48]</td>
<td>+ [55]</td>
</tr>
</tbody>
</table>

*Data from randomized, double-blind, placebo-controlled trials.
+*: therapeutic effect (number indicates relative magnitude); –*: no therapeutic effect; NA: data not available or not yet investigated; TNF: tumor necrosis factor.

Tuberculosis

An initial analysis of patients reported to have developed TB while taking anti-TNF-α drugs demonstrated a predictable pattern of disease for patients who were immunosuppressed [12]. Most of the patients developed extrapulmonary TB disease, and nearly a quarter had disseminated disease. In contrast, among immunocompetent persons, 15% developed extrapulmonary disease and <1% had disseminated disease [13]. Wolfe et al. recently compared the background TB incidence in patients with RA (in 1998–1999) and the incidence in those treated with infliximab (2000–2002) in the US [14]. The background TB incidence was 6.2 cases per 100 000 patients during 1673 patient-years of observation, while the incidence for infliximab-treated RA was 52.2 cases per 100 000 patient-years of exposure [14]. Data from EU post-approval studies have also yielded a higher rate of TB in infliximab-treated patients than the background rate of TB in RA [3]. In the case of adalimumab, a dose–response association between the drug and TB has been observed: more patients reactivate TB on a higher dose of the agent, and less TB reactivation has been observed in patients on a lower dose if no prior screening for TB has been performed [15]. In contrast, fewer cases of TB have been reported after the use of etanercept [16,17]. These observations have led to a series of studies investigating the mechanisms of action of TNF-α blockers that might explain the different incidence of infections during therapy.

Mechanisms of action

These differences include not only the spectrum and rate of side effects, but also the range of diseases for which each agent has proven therapeutic efficacy (Table 1). Properties that may contribute to the differences between antibodies and soluble receptors in terms of efficacy and side effects are discussed below.

In terms of the binding properties of the agents, infliximab is able to bind soluble TNF-α, transmembrane TNF-α, and receptor-bound TNF-α, forming a relatively stable complex; however, it does not bind TNF-β (lymphotoxin). Of note, in vitro binding to the membrane-bound form might lead to cell lysis, possibly explaining the drop in monocyte number that has been seen after infliximab administration [18,19]. Adalimumab forms stable complexes with TNF-α and is also able to induce cell lysis in vitro in the presence of complement; like infliximab, it does not bind TNF-β. Unlike the antibodies, etanercept can bind to both TNF-α and TNF-β, but interacts with membrane-bound TNF with a lower affinity than infliximab, and is not able to activate complement or lyse cells expressing membrane-bound TNF-α. In addition, etanercept binding is reversible, and dissociated TNF remains bioactive [18]. Although etanercept is constructed with the complement receptor domains of human immunoglobulin G1, one of the CH3 groups at the hinge region of the fusion of the Fc chain to the p75 extracellular domain of the TNF receptor is missing. The extent to which the deleted CH3 could explain the differences in binding properties between etanercept and the antibodies is unclear.

The development of infections, especially TB, in patients receiving TNF-α blockers represents a serious concern; therefore, guidelines for assessing risk and managing TB infection in patients due to start anti-TNF-α treatment have been developed [20]. Screening for latent TB infection—which includes taking a history of exposure to Mycobacterium tuberculosis, a tuberculin skin test, and a chest radiograph—

Table 1. Therapeutic spectrum and effectiveness of the main TNF-α-blocking agents currently marketed.
is advised in all patients before the use of TNF-α blockers, especially adalimumab and infliximab [20]. The impact of screening for latent TB infection prior to initiating TNF-α blocker therapy has been reported recently. Perez et al. [21] and Gomez-Reino et al. [22] have suggested a consistent reduction in TB reactivation after screening according to the guidelines.

Demyelinating disorders
Treatments with TNF-α-blocking agents have been associated with rare cases of onset or exacerbation of demyelinating disorders, with partial or complete remission after stopping treatment [23,24]. Myelitis, optic neuritis, multiple sclerosis (MS), and seizure disorders have been observed in association with etanercept therapy [24]. In addition, despite the elevated concentrations of TNF-α in the cerebrospinal fluid and circulatory system of patients with MS, blocking this cytokine resulted in a worsening of the disease [23]. The mechanisms underlying this side effect are unknown.

Lupus-like syndrome
 Antibody formation can follow the administration of biological agents such as the TNF-α blockers. Immunological reactions that can occur with TNF-α blockade include the development of autoantibodies and neutralizing and non-neutralizing antibodies. The development of autoantibodies, including antinuclear antibody and anti-double-stranded DNA, has been reported during therapy with anti-TNF-α agents [24,25]. The clinical relevance of this is uncertain, but post-marketing surveillance reports mention cases of autoimmune diseases, especially leukocytoclastic vasculitis and lupus-like syndrome, improving after the discontinuation of therapy [25].

Malignancies
Because of the immunosuppressive character of TNF-α blockade, the development of malignancies in anti-TNF-α-treated patients may occur. For solid tumors, the incidence is comparable to the age-, sex-, and ethnicity-matched rate in the general population [26]. However, an increased incidence of lymphomas has been observed in patients with RA [27], and concerns have been raised regarding the risk of these malignancies, especially non-Hodgkin’s lymphoma, during therapeutic TNF-α blockade [28]. The standardized incidence ratio (SIR) of lymphoma within large cohorts of patients with RA is approximately 2.0–2.7 [29,30]. This risk has been shown to correlate with the activity and severity of disease, as well as exposure to immunosuppressive agents. In anti-TNF-α therapy, data from clinical trials revealed an SIR that varied from 3.47 in the case of etanercept, to 4.35 with adalimumab, and 6.4 in infliximab-treated RA patients [1]. However, post-approval studies did not confirm these high rates of lymphomas among anti-TNF-α-treated patients, possibly due to under-reporting of lymphoma [28].

A recent meta-analysis of nine published randomized controlled studies of adalimumab- and infliximab-treated patients with RA indicated a dose-dependent increased risk of malignancies in these patients compared with placebo groups [26]. The authors did not find an accumulation of malignancies with longer therapy duration, suggesting that TNF-α blockade is likely to accelerate the development of pre-existing subclinical malignancies rather than inducing new malignancies [26].

Congestive heart failure
The leading cause of death in RA is cardiovascular (CV) disease, which accounts for approximately one-third to one-half of all RA-related deaths [31,32]. In addition, patients with RA have twice the risk of developing congestive heart failure (CHF), which is not explained by traditional CV risk factors or clinical ischemic heart disease. A recent study by Nicola et al. assessing the contribution of CHF and ischemic heart disease to excess mortality in RA concluded that the elimination of excess risk of CHF in patients with RA could significantly improve their survival rate [33]. In this context, assessment of the CV effects of any new therapy in RA is warranted.

Previous studies have indicated that there is an association between CHF and elevated production of TNF-α; therefore, it was postulated that there could be an improvement of heart failure upon TNF-α blockade [34]. However, when etanercept and infliximab were tested in trials to determine the effects of suppressing TNF-α in patients with CHF, an increased mortality rate was observed in the anti-TNF-α groups compared with the placebo groups [35]. In particular, the combined endpoint of all-cause mortality or hospitalization for heart failure after 28 weeks had a hazard ratio of 2.84 in patients randomized to 10 mg/kg infliximab compared to those given placebo [35].

The current literature suggests that the incidence and prevalence of heart failure among patients with RA who are treated with TNF-α antagonists are the same as in those who do not receive this therapy [36]. However, the US Food and Drug Administration (FDA) has recently reported 47 cases of new or worsening CHF in patients receiving anti-TNF-α therapy for RA or Crohn’s disease: 38 patients (26 on etanercept and 12 on infliximab) developed new-onset CHF; and nine (three on etanercept and six on infliximab) experienced exacerbation of CHF. Nineteen (50%) of the 38 patients with new-onset CHF (12 on etanercept and seven on infliximab) had no identifiable risk factors. In 10 patients aged <50 years, new-onset CHF developed after receiving a TNF-α antagonist. After the TNF-α antagonist
was discontinued and therapy for heart failure was initiated, three patients experienced complete resolution of CHF, six improved, and one died [3]. These results need to be interpreted with caution as they were reported to the FDA MedWatch, which is a passive surveillance program. However, on the basis of the current literature and these data, it is recommended that TNF-α blockers should be avoided in patients with CHF, especially those who have New York Heart Association functional class III or IV heart failure.

Perhaps more interestingly, therapy with TNF-α blockers may have beneficial consequences in addition to those related to inflamed joints in patients with RA. The importance of the contribution of inflammation to the development of atherosclerosis and insulin resistance is being increasingly appreciated, and TNF-α has emerged as playing a key role in these processes. In addition, markers of inflammation such as C-reactive protein (CRP) are now considered to be important predictors of future acute CV events. Consequently, our group recently investigated whether the profile of CV risk factors in patients with RA is ameliorated during anti-TNF-α treatment [37]. This would not be unexpected, since TNF-α is known to increase IL-6 and CRP levels and to induce pro-atherogenic changes in lipid profiles. Accordingly, it was found that anti-TNF-α treatment with adalimumab enhanced the concentration of high-density lipoprotein cholesterol and decreased the concentrations of CRP and IL-6 within 14 days. The extent to which these changes would remain over a prolonged observation period and translate into a lowered CV risk is unclear; this is a subject for future studies.

Conclusion
In conclusion, as is the case with any immunosuppressive therapy, safety considerations with anti-TNF-α agents remain an important issue. Despite their side effect profiles, anti-TNF-α agents have a very good risk–benefit ratio. However, caution is warranted when these drugs are given to patients who already have an increased risk of developing any of the complications seen with these agents.

Disclosure
The authors do not have any relevant financial interests to disclose.

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Atypical Polymyalgia Rheumatica: A Clinical Conundrum

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Polymyalgia rheumatica (PMR) is a clinical syndrome of uncertain etiology characterized by morning stiffness and pain in the shoulder, the pelvic girdle, or both [1]. As with most rheumatic conditions, there is no single diagnostic test, although the acute-phase proteins are usually elevated. Proposed criteria are relatively non-specific (Table 1) [2], and the diagnosis is usually made on clinical grounds, with supporting laboratory findings.

Here, the author discusses three cases where PMR was suspected, but further investigation revealed significant alternative diagnoses. All three presented to a single district hospital within a 4-month period.

Case 1
A 73 year old Caucasian female was routinely referred by her general practitioner (GP) to a rheumatology outpatient clinic with pain and stiffness around her hips over a 6-month period. Symptoms were symmetrical and at their worst in the morning. There were no shoulder or neck pains, and no constitutional symptoms. Her medical history included diverticulitis, cataracts, hypertension, ischemic heart disease, and osteoarthritis of the right hip. She had developed erythema nodosum 12 months previously, with proven streptococcal infection, and this had subsequently resolved. The patient had stopped taking simvastatin of her own accord after reading the product information leaflet, with no symptomatic improvement.

The GP arranged for some routine blood tests. Full blood count, urea level, electrolyte level, and liver function were all normal; the erythrocyte sedimentation rate (ESR) was 35 mm/h and the C-reactive protein (CRP) level was 5 mg/L. Prednisolone 20 mg/day was started for presumed PMR. However, the patient failed to show any clinical response and was referred to a rheumatologist for advice regarding further management.

In clinic 4 weeks later, the principal complaint was of pain and stiffness around the right groin with lesser symptoms on the left. Upper limb symptoms were not reported and a full systems review revealed that the patient had developed abdominal bloating and increased shortness of breath on exertion. Examination revealed well-preserved joints for her age with minor osteoarthritic signs in the right hip. There was also slight bilateral tenderness of the plantar fascia. Cardiorespiratory examination findings were unremarkable but she did have a distended abdomen, with high-pitched bowel sounds. At this time, the CRP level was 140 mg/L, with normal renal and hepatic function. Autoantibodies and vasculitis screening test results were negative.

An urgent computed tomography (CT) scan of the chest, abdomen, and pelvis was requested, which showed a large pancreatic carcinoma with evidence of omental metastases, and chest sequences surprisingly demonstrated multiple...
pulmonary emboli. She was immediately admitted to hospital and given anticoagulation treatment, but suffered a respiratory arrest and died the same day.

**Case 2**

An 86 year old Caucasian male was referred urgently to the rheumatology clinic with persistent low backache, pelvic pain, and stiffness. Four years previously he had been diagnosed with PMR following presentation with bilateral neck, shoulder, and upper arm pain, and morning stiffness. The ESR was 69 mm/h at initial presentation and he had a prompt and complete response to prednisolone 15 mg/day. His prednisolone usage had been gradually tapered and then stopped 2 months previously. His current symptoms paralleled a withdrawal of corticosteroid therapy.

The reason for his referral for specialist assessment was to determine whether he had had a recurrence of PMR and to obtain advice regarding further therapy. Closer questioning revealed predominant right-sided symptoms and no shoulder or neck pain. His appetite was poor and he had lost approximately 13 kg in weight over the previous 4–6 months. He did not report morning stiffness; his symptoms were continuous throughout the day.

Other elements of his medical history included hypothyroidism and transitional cell carcinoma (TCC) of the bladder, which involved a G3pT1 tumor, 9 years previously. This had been treated with resection and radical radiotherapy, with no evidence of recurrence on continuing annual cystoscopy.

Blood tests by the GP revealed a normochromic normocytic anemia with a hemoglobin level of 10.4 g/dL, normal levels of urea and electrolytes, an ESR of 55 mm/h, and a CRP level of 40 mg/L. A lumbar spine radiograph arranged by the GP showed generalized osteopenia and evidence of superior endplate depression at a number of levels in the lumbar vertebrae consistent with osteoporotic collapse. The patient’s pain was increasing despite opiate analgesia, and he was admitted to hospital, but general findings were unremarkable. His hips and lumbar spine were surprisingly normal on examination, with a full range of movement and normal straight leg raise and femoral nerve stretch test results. There was no muscle tenderness, and urinalysis and rectal examination results were normal.

In view of the patient’s history, an isotope bone scan was requested. This showed no focal increased uptake in the spine but did show photopenia in the right kidney (Fig. 1). A subsequent CT scan showed a right-sided lumbar paraspinal mass, which had distorted the pedicle of the right kidney. Biopsy demonstrated a poorly differentiated TCC of the bladder. The patient is currently receiving palliative radiotherapy.

**Case 3**

A 55 year old Caucasian female was referred to a rheumatology outpatient clinic with right hip and thigh pain, anemia, and raised inflammatory marker levels. This had started 8 months previously as a dull lower abdominal ache that was worst in the morning and after rest. The GP had requested a pelvic ultrasound, the results of which were normal, and had referred the patient to the colorectal surgeons, who had discharged her following normal upper and lower gastrointestinal tract endoscopy findings. There was no change in bowel habit, no urinary symptoms, no cough, no anorexia, and no nausea, but she began to feel increasingly lethargic and breathless on exertion. Her inflammatory marker levels were rising and the GP felt that the thigh pain, fatigue, and anemia may be accounted for by PMR. Her medical history included total abdominal hysterectomy for menorrhagia, varicose veins, migraine, and polymorphous light eruption. However, a challenge with corticosteroid offered little therapeutic benefit.

In clinic, despite a comprehensive systems review, there was nothing specific in the history to add; cardiovascular, respiratory, and abdominal examination findings were unremarkable. There was no clubbing, lymphadenopathy, or focal neurology, and facies were normal. Joint examination findings were also unremarkable and there was no muscular pain or tenderness. Urinalysis results, white cell count, and platelet levels were normal, and the hemoglobin was normochromic and normocytic, and at a level of 9.4 g/dL. Liver and thyroid function, levels of electrolytes, calcium, and immunoglobulins, and autoimmune screening...
results were all normal. The CRP was 142 mg/L and ESR 125 mm/h.

An urgent isotope bone scan was requested. This showed a normal skeleton but an area of photopenia in the upper pole of the right kidney. A CT scan of the abdomen demonstrated a large tumor of the right kidney, with local extension into the adrenal gland, causing compression and thrombus of the inferior vena cava (IVC). This was suitable for resection, and she had a radical right nephrectomy and IVC thrombectomy. Histopathology showed a grade 4 renal cell carcinoma with a tumor at the hilar margin of the resection site. She has recovered well post-operatively and is currently awaiting adjuvant immunotherapy.

**Discussion**

PMR is perhaps the most common vasculitic disorder of older patients encountered in primary care [3]. Its incidence is higher in more northern latitudes, and one UK study found a prevalence of 3.3% in patients aged >65 years in a primary care setting [4]. From what was once an overlooked entity, PMR may now have become over-diagnosed [5].

The cases presented here highlight some of the difficulties in assessing patients with possible PMR. All of the above were referred to secondary care because, although there was clinical suspicion of PMR, the clinical features or therapeutic response had been atypical.

In particular, case 1 had a low acute-phase response and failed to respond to a corticosteroid challenge, which alerted the GP to question the diagnosis and refer appropriately. Sadly, the non-specific presentation, with the absence of localizing symptoms and signs hindered an earlier diagnosis and the chance of intervention.

Case 2 had atypical, asymmetrical pain, with no morning stiffness. Notably, the symptoms were markedly different from those of the previous presentation, which was successfully treated as PMR with low-dose corticosteroids. However, the onset appeared to coincide with corticosteroid withdrawal, hence raising a suspicion of PMR recurrence. Equally, the patient was under continued cystoscopy surveillance from the urology team, which had reliably shown an absence of local recurrence. The patient’s constitutional symptoms were disproportionate to the musculoskeletal symptoms and signs, hence the need for further investigation.

Case 3 again had asymmetric pain with relative lack of morning stiffness or typical limb girdle symptoms; however, the patient was systemically unwell. It should also be noted that urinalysis results had been negative in both case 2 and case 3 on more than one occasion, which diverted clinical suspicion to other systems. However, the Bird criteria (Table 1) were fulfilled in each case.

<table>
<thead>
<tr>
<th>Table 2. Differential diagnosis of polymyalgia rheumatica.</th>
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<tbody>
<tr>
<td><strong>Neoplastic disease</strong></td>
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<tr>
<td><strong>Joint disease</strong></td>
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<tr>
<td>• Osteoarthritis, especially of the cervical spine</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
</tr>
<tr>
<td>• Connective tissue disease</td>
</tr>
<tr>
<td>• Mechanical shoulder disease</td>
</tr>
<tr>
<td><strong>Hematological disorders</strong></td>
</tr>
<tr>
<td>• Multiple myeloma</td>
</tr>
<tr>
<td>• Leukemia</td>
</tr>
<tr>
<td>• Lymphoma</td>
</tr>
<tr>
<td>• Myelodysplasia</td>
</tr>
<tr>
<td><strong>Muscle disease</strong></td>
</tr>
<tr>
<td>• Polymyositis</td>
</tr>
<tr>
<td>• Atypical myopathies</td>
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<tr>
<td><strong>Infections</strong></td>
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<tr>
<td>• Subacute bacterial endocarditis</td>
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<tr>
<td>• Mycobacterial infections</td>
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<tr>
<td>• Fungal infection</td>
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<tr>
<td><strong>Bone disease</strong></td>
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<tr>
<td>• Osteomyelitis</td>
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<tr>
<td><strong>Parkinsonism</strong></td>
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<td><strong>Hypothyroidism</strong></td>
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<td><strong>Functional</strong></td>
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</table>

The difficulty of diagnosis in all three cases lies in the lack of localizing symptoms and signs. It should be noted that case 2 and case 3 had normal urological histories and examination results. In each case, multiple urine dipstick test results were normal. Case 1 failed to exhibit any classical signs of pulmonary embolism, with no chest pain, gradual breathlessness, or signs of peripheral thrombosis. Essentially, each case presented was non-specifically unwell with raised acute-phase marker levels.

The diagnosis of PMR when presentation is not typical should be considered one of exclusion. The differential diagnosis for patients presenting with stiffness, pain, and a raised ESR or CRP level is wide, especially in older people (Table 2). In particular, confusion with PMR has also been reported for prostate [6], breast [7], colon [8], and hematological cancers [9], among others. One small observational study found as many as 10% of primary care referrals for evaluation of PMR in fact had a malignancy [10]. However, this figure is likely to be influenced heavily by referral bias, with most patients who have a simple uncomplicated course being cared for in the primary care setting. While it may be satisfying to make a diagnosis of PMR and observe the dramatic response to low-dose corticosteroid therapy, the presence of atypical features may highlight an underlying neoplasm. Reported associated
features include asymmetry of involvement, distal involvement, absence of prolonged morning stiffness, lack of raised inflammatory markers, and inefficacy of corticosteroids. In particular, failure of either the symptoms or inflammatory markers to respond to adequate doses of corticosteroids should alert the clinician to the possibility of an alternative diagnosis and the need to consider further investigation or appropriate referral. However, up to 25% of patients with PMR present with atypical features [10]. It is important that all patients have a full clinical examination, including palpation for lymphadenopathy and a prostate examination if applicable [6]. Some further investigations for a patient presenting with non-specific symptoms and raised levels of acute-phase markers are outlined in Table 3.

The prompt and efficient treatment for classical cases of PMR should undoubtedly not be delayed by needless investigation. Nonetheless, a proportion of patients treated initially for PMR may have an underlying malignant disorder, especially those who fail to respond promptly to therapy.

Case Study Editor’s comment
The cases here outline a frequent problem encountered in rheumatology that relates to the lack of specific diagnostic tests for most of the conditions that are treated. Hence, the diagnosis relies on history, examination, and appropriate further investigation. Patients most often present with features “compatible with”, rather than fulfilling, diagnostic or classification criteria. With earlier intervention, pathognomonic features of diseases that are encountered are less frequently seen.

There is an old saying: “He who has the best view has seen the thing from the start.” This is highly relevant to rheumatology, where initial presentation and investigation can be crucial to further management. Once corticosteroids have been started, disease-specific characteristics and laboratory test results may be altered, especially if inappropriately high doses are used.

The majority of PMR cases referred to hospital in the UK are “atypical”, where the diagnosis is uncertain or where corticosteroid withdrawal is proving difficult within a reasonable timescale; such cases always prove troublesome. Frequently, corticosteroid withdrawal, clinical reassessment, and further investigation are required, despite the fact that this results in temporary suffering for the patient. At this stage, the clinician is dealing with not only an uncertain diagnosis, but also corticosteroid dependence and side effects.

The cases here highlight the required vigilance for atypical disease features and, perhaps most importantly, the lack of a marked therapeutic response to corticosteroids; a dramatic response may be the most distinguishing feature of PMR.

### Table 3. Possible investigations for unexplained joint pain, stiffness, and raised acute-phase response.

<table>
<thead>
<tr>
<th><strong>Baseline</strong></th>
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</thead>
<tbody>
<tr>
<td>Full blood count, electrolytes, creatinine, and creatine kinase</td>
</tr>
<tr>
<td>Autoantibody profile</td>
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<tr>
<td>Serum electrophoresis or urinary Bence–Jones protein</td>
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<table>
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<tr>
<th><strong>Immunology</strong></th>
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<tbody>
<tr>
<td>Antinuclear cytoplasmic antibodies</td>
</tr>
<tr>
<td>Anticardiolipin antibody</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
</tr>
<tr>
<td>Specific extracted nuclear antibodies</td>
</tr>
<tr>
<td>Paraneoplastic antibodies</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Imaging</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal ultrasound</td>
</tr>
<tr>
<td>Computerized tomography – lymphoma protocol</td>
</tr>
<tr>
<td>Nuclear medicine – isotope bone scan or labeled white cell scan</td>
</tr>
<tr>
<td>Magnetic resonance imaging or magnetic resonance angiography</td>
</tr>
<tr>
<td>Plain radiography – skeletal survey</td>
</tr>
<tr>
<td>Angiography – celiac plexus, renal, or aortic arch</td>
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</tbody>
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<table>
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<tr>
<th><strong>Infection screen</strong></th>
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</thead>
<tbody>
<tr>
<td>Atypical findings from serology, virology, or mycobacterial culture or polymerase chain reaction</td>
</tr>
<tr>
<td>Urine, sputum, blood, or stool cultures, and microscopy for spores</td>
</tr>
<tr>
<td>Throat swab</td>
</tr>
<tr>
<td>Streptococcal or staphylococcal serology</td>
</tr>
<tr>
<td>Endemic serological testing as appropriate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Other</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy (upper and lower gastrointestinal tract to include biopsy), bladder, or bronchoscopy and lavage</td>
</tr>
<tr>
<td>Bone marrow examination and culture</td>
</tr>
<tr>
<td>Genotyping – HLA-B27</td>
</tr>
<tr>
<td>Tumor markers</td>
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</tbody>
</table>

### References

Clinical reviews were prepared by Tom Huizinga, Eric Ruderman, and Hendrik Schulze-Koops

**TREATMENT STRATEGIES**

**Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study**


This study of 266 patients treated with anti-tumor necrosis factor-α agents reveals that the antibodies (i.e. adalimumab and infliximab), but not etanercept, appear to decrease the risk of uveitis flares in patients with spondyloarthropathy.

Tumor necrosis factor-α (TNF-α) antagonists have become an important tool in the management of spondyloarthropathies, manifestations of which include inflammatory uveitis. In this study, the authors conducted a retrospective review of all patients with spondyloarthropathy at a single center (Cochin Hospital, Paris, France) who were treated with anti-TNF-α therapy and had at least one flare of uveitis. Their goal was to determine the impact of anti-TNF-α therapy on uveitis flares.

Among 266 patients treated with TNF-α antagonists for their spondyloarthropathy during a 7-year period, the authors identified 46 patients who had a history of uveitis and for whom follow-up information was available for ≥1 week after the initiation of anti-TNF-α therapy. Of these patients, 25 were treated with infliximab, 13 with etanercept, and eight with adalimumab. Clinical information was available for a mean of 15.2 years prior to initiation of anti-TNF-α therapy and 1.2 years after it was started.

Overall, the number of uveitis flares was 51.8 per 100 patient-years before anti-TNF-α therapy and 21.4 per 100 patient-years while on therapy (p=0.03). However, the soluble TNF-α receptor etanercept had no impact on uveitis flares, which occurred at a rate of 54.6 per 100 patient-years before therapy and 58.5 per 100 patient-years after it was started (p=0.92). The length of follow-up for patients treated with adalimumab was shorter, and no patients had a flare of uveitis after starting treatment; therefore, the flare rate could not be calculated. However, when data from patients treated with adalimumab and infliximab (the two anti-TNF-α antibodies) were pooled, a significant reduction was found in uveitis flares with therapy, from 50.6 per 100 patient-years before the start of treatment to 6.8 per 100 patient-years afterwards (p=0.001). The number of patients needed to be treated with anti-TNF-α antibody therapy to avoid a single uveitis flare was just two.

These data suggest that anti-TNF-α therapy can reduce the risk of uveitis flares occurring in patients with spondyloarthropathies, but that this reduction is seen with anti-TNF-α antibody therapy and not with etanercept. The number of patients treated with adalimumab was too low and their follow-up period too short to determine whether the effect of reducing uveitis flares differed between the two antibodies. These results, if confirmed in other populations, could have important implications for the choice of anti-TNF-α therapy in patients with spondyloarthropathy who have recurrent uveitis.

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**Self management of arthritis in primary care: randomised controlled trial**


This large study adds to the literature on self-management programs for patients with osteoarthritis; the findings revealed some benefits but no improvements in pain, function, or quality of life.

Self-management programs have been developed to help the increasing numbers of patients with arthritis to cope with the disease and its effects. In this randomized study, the authors studied the impact of an arthritis self-management program on a group of patients with osteoarthritis from primary care practices in the UK.
Rheumatology (Oxford) 2006; Brandt KD, Mazzuca SA, Buckwalter KA. Acetaminophen, like conventional NSAIDs, may reduce synovitis in osteoarthritic knees

Patients with knee osteoarthritis generally seek medical help for pain. In this small study, the effects on pain were similar in patients treated with acetaminophen and in those treated with nonsteroidal anti-inflammatory drugs. Intriguingly, the effect on joint swelling (synovial effusion volume and synovial tissue volume), as measured by magnetic resonance imaging, were also similar for the two groups of patients.

In this study of patients with knee osteoarthritis who were treated with nonsteroidal anti-inflammatory drugs (NSAIDs; n=20) or acetaminophen (n=10), a disease flare was induced by stopping the medication. In each group, the mean total effusion volume during flare was approximately 16 mL.

After reintroducing the medication, comparable and significant decreases in effusion volume were observed in the NSAID-treated patients (~4.5 mL; p=0.009) and the acetaminophen-treated patients (~3.3 mL; p=0.013). In addition, the mean decrease in Western Ontario McMaster Universities Osteoarthritis Index pain score recorded after the reintroduction of NSAID treatment was comparable to that recorded after the reintroduction of acetaminophen treatment (~9.6 and ~9.0, respectively).

Given the evidence that acetaminophen does not exhibit anti-inflammatory actions, the authors proposed that the observed effects were mediated by inhibition of nociceptor-induced neurogenic inflammation. Support for this explanation can be found in the dental literature, which also contains reports of the anti-inflammatory effects of acetaminophen [1].


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Comparing the long-term clinical outcome of treatment with methotrexate or sulphasalazine prescribed as the first disease-modifying antirheumatic drug in patients with inflammatory polyarthritis


This study compared clinical outcomes in patients treated with either methotrexate (MTX) or sulphasalazine as the first disease-modifying antirheumatic drug. The two treatments were associated with similar long-term clinical outcomes, although MTX was potentially more effective in preventing the development of erosions.

Early treatment for patients with rheumatoid arthritis (RA) using disease-modifying antirheumatic drugs (DMARDs) improves their long-term clinical outcome. This study aimed to directly compare the efficacy of methotrexate (MTX) and sulphasalazine (SSZ) as the first DMARD in patients with early inflammatory polyarthritis (n=439). These patients, 331 of whom received SSZ and 108 of whom were given MTX as the first DMARD, were recruited from the Norfolk Arthritis Register (Norfolk, UK) over a 10-year period and were followed for 5 years. Over the 10-year recruitment period, there was a clear trend toward starting DMARD treatment with fewer active joints and using MTX as the first DMARD.

The clinical and functional outcomes of the SSZ and MTX groups were compared using:
• Swollen and tender joint counts (SJCs and TJCs) at 2 and 5 years.
• The Health Assessment Questionnaire (HAQ) at 2 and 5 years.
• C-reactive protein (CRP) levels at 5 years.
• The 28-joint Disease Activity Score (DAS28) at 5 years.
• Larsen scores at 5 years.

Baseline CRP levels, DAS28 values, and HAQ scores were similar for the two groups, whereas patients starting with SSZ were younger and had higher SJCs and TJCs. Propensity scores were used to overcome potential bias in the baseline parameters.

There were similar declines in the two treatment groups in SJCs, TJCs, and HAQ scores at both 2 and 5 years, and there were similar changes in CRP levels and DAS28 values at 5 years. At 2 years, more patients in the MTX group than the SSZ group remained on their first DMARD (56% vs. 50%), and this trend persisted at 5 years (34% vs. 22%). MTX treatment was associated with a reduced incidence of erosions (odds ratio 0.3, 95% confidence interval 0.1–0.8) and a 31% lower Larsen score (not significant), compared with the SSZ group at 5 years.

In summary, patients starting their treatment with MTX and those starting their treatment with SSZ had similar long-term clinical outcomes, although MTX was potentially more effective in preventing the development of erosions.

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Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipment
Koski JM, Saarakkala S, Helle M et al.

Ultrasound is a sensitive tool for detecting synovial inflammation but the results of this study demonstrate that it is unable to reliably quantify this inflammation.

As more therapies become available for the management of rheumatoid arthritis (RA), there is increasing pressure to develop reliable ways to measure treatment response. Ultrasonography has been proposed as a more sensitive tool for measuring synovitis than the clinical examination. In this study, the authors use histopathological evaluation of synovial tissue biopsy samples as the gold standard by which to measure the utility of ultrasonography for measuring the presence and severity of synovitis.

Forty-four patients scheduled for synovial biopsy to evaluate their inflammatory arthritis underwent ultrasound examination prior to an ultrasound-guided biopsy with three

In a study of the treatment preferences of patients with osteoporosis (n=212), it was found that the bisphosphonates were the most popular treatment; furthermore, there was a preference for annual infusions rather than weekly oral administration.

Osteoporosis is a common disease: approximately 50% of women and 25% of men will have an osteoporotic fracture during their lifetime. However, many patients will not receive any benefit from treatment. For example, if 100 women aged 75 years with osteoporosis took alendronate, 11 fractures would be prevented and 11 fractures would occur despite treatment, assuming a 10-year probability of sustaining a hip fracture of 22%. Therefore, of 100 patients given treatment, 89 receive no benefit. Given these data, patient preference is of utmost importance.

Patients who had recently undergone bone densitometry were recruited if they had osteoporosis or a Fracture Index score ≥6 (the threshold for medical intervention). All patients underwent questionnaires to determine preferences for weekly oral bisphosphonates, annual intravenous bisphosphonates, or daily subcutaneous recombinant human parathyroid hormone (rhPTH). Simulations of patient preferences were based on three aspects:

• Respondent values for route of administration.
• Absolute reduction in risk of fractures over 5 years.
• Risk of adverse effects.

In the simulations, the majority of patients preferred bisphosphonates, and preferences changed little when the benefits of rhPTH were widened to incorporate its increased effectiveness compared with bisphosphonates. The reported preference for annual intravenous injections is important when considering long-term treatment, given the poor rates of adherence to osteoporosis medications.

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different machines. All scans were performed by the same operator and included both gray-scale ultrasound and power Doppler imaging, with the latter used to assess blood flow (which is believed to be a marker of inflammatory activity). Patient diagnoses were varied and included RA, psoriatic arthritis, and unspecified mono- and polyarthritis.

In all, 35 of the 44 biopsy samples revealed active synovitis; an additional eight patients had other synovial abnormalities, for a total of 43 abnormal biopsy samples. Gray-scale ultrasound examination detected either synovial proliferation or effusions in 42 patients. However, there was no correlation between a semi-quantitative histological scoring of the synovial biopsy tissue and the findings on ultrasound. Power Doppler ultrasound examinations showed a positive signal in 34 patients. Again, the strength of the Doppler signal did not correlate with the histological score, although it did correlate with the level of subsynovial neutrophil infiltration. In one case of severe histological inflammation, there was a negative Doppler signal, and the Doppler signal did not distinguish between synovitis and other synovial abnormalities. Finally, the authors found that the three ultrasound devices tested differed in their ability to detect synovial blood flow.

The authors conclude that ultrasound examination, including power Doppler imaging, is a sensitive tool for detecting synovial inflammation, but they question the ability of this technique to quantify the degree of inflammation. These data cast doubt on the utility of ultrasound imaging in monitoring response to therapy of inflammatory arthritis.

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Evaluation of a modified ACR20 scoring system in patients with rheumatoid arthritis receiving treatment with etanercept
Goldman JA, Xia HA, White B et al.

Modified ACR20 scoring systems that excluded one or two acute-phase reactant criteria were shown to be consistent with the standard ACR20 score, based on data from early rheumatoid arthritis (RA) and late RA clinical trials.

The American College of Rheumatology (ACR) score provides an efficacy endpoint for clinical trials in patients with rheumatoid arthritis (RA) that evaluates clinical improvement relative to an initial assessment. The ACR20 score denotes ≥20% improvement in tender and swollen joints and in three of the following endpoints:

- Global assessment by patients.
- Global assessment by doctor.
- Erythrocyte sedimentation rate or C-reactive protein level.
- Self-reported visual analogue scale for pain.
- Health Assessment Questionnaire score.

In the present study, the standard ACR scoring system was compared with two modified ACR (mACR) scoring systems that excluded one or two acute-phase reactant criteria. The different scoring methods were evaluated using data from clinical trials on methotrexate (MTX)-naïve patients with early rheumatoid arthritis (RA) and patients with disease-modifying antirheumatic drug-refractory late RA. The patients with early RA were randomly assigned to receive MTX, etanercept (ETN) 10 mg twice weekly, or ETN 25 mg twice weekly, whereas the patients with late RA received placebo, ETN 10 mg twice weekly, or ETN 25 mg twice weekly. The standard ACR20 scores were calculated and compared with mACR20 scores for both patient groups, using full joint counts and 28-joint assessments.

The clinical trials included 632 patients with early RA and 234 patients with late RA. The patients were mostly Caucasian women receiving nonsteroidal anti-inflammatory drugs at baseline. In the early RA trial, significantly more patients in the ETN 25 mg group than in the ETN 10 mg group were deemed to be ACR20 responders using full joint counts (p<0.01). Similar differences between these two groups were seen for the two mACR20 scores. The same pattern was found with the 28-joint counts. In the late RA trial, considerably more patients achieved a clinical response in both ETN groups than in the placebo group using the ACR20 and the two mACR20 scoring systems with both full joint counts and 28-joint counts (all p<0.001).

The only differences between the ACR20 and the mACR20 scoring systems were observed in the early RA trial, in comparisons of the ETN 10 mg and the MTX group. Whereas the mACR20 scores indicated significant differences between the ETN 10 mg and the MTX group, the ACR20 score did not reveal such differences.

When comparing the early RA and late RA patient group, the overall pattern of improvement indicated by mACR20 scores was consistent with that indicated by the standard ACR20 scores. Overall, the results suggest that the mACR20 scoring systems can be used to assess group efficacy response when the acute-phase reactant values are not available.

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Comment on the use of self-reporting instruments to assess patients with rheumatoid arthritis: the longitudinal association between the DAS28 and the VAS general health


This analysis of two observational cohorts suggests that objective outcome measurements and patient self-report describe different, but equally important, elements of rheumatoid arthritis disease activity.

Patient-reported outcomes are increasingly recognized as important tools in disease assessment and measurement of response to therapy in rheumatoid arthritis (RA). Some authors have recently suggested that a combination of self-reported instruments may be as useful as objective measurements of disease activity in distinguishing between an active drug and placebo in clinical trials. In this article, the authors report on a series of patients with newly diagnosed RA followed over 3 years and suggest that there may be fundamental limitations to the use of self-reported data to indicate disease activity over time.

Two observational cohorts of patients with newly diagnosed RA (time since diagnosis <1 year) in The Netherlands were used for the analysis. The primary objective outcome measured was a variation of the 28-joint Disease Activity Score (DAS28) that included both tender and swollen joint counts and the sedimentation rate, but not the visual analogue scale (VAS) for general health. Self-reported outcomes included VAS measurements for general health, pain, and disease activity, and the Health Assessment Questionnaire (HAQ).

The cohort studied included 624 patients who had completed 3 years of follow-up. The authors found a strong association between the VAS for general health and the DAS28 at all time points, but the relationship between the two outcomes differed over time, with patients reporting better general health for the same level of disease activity later in their disease course. The authors also found that self-reported general health improved over time, independent of the DAS28, but that function, measured by the HAQ, declined over time, despite a general improvement in disease activity.

This study suggests that the relationship between objective measures of disease activity and patients' self-perception of disease differs depending on the duration of disease. In particular, self-reported health is better for a given level of disease activity later in the disease course, perhaps owing to adaptation or changing expectations. HAQ scores showed the opposite effect, with a relative increase (worse function) when compared with a given level of disease activity at later timepoints, possibly reflecting the impact of damage, rather than activity, on function. Overall, this study suggests that both objective measurements and patient self-report are necessary to give a true picture of the impact of RA, as well as the response to therapy.

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MRI of the sacroiliac joints in patients with moderate to severe ankylosing spondylitis


The availability of new treatment options for ankylosing spondylitis (AS) is making reliable methods for assessing disease activity even more important. Findings from this study indicate that magnetic resonance imaging, while sensitive in the detection of sacroiliitis in AS, does not appear to be a useful marker of clinical disease activity.

As new treatment options for ankylosing spondylitis (AS) become available, it is important to have reliable methods for assessing disease activity. Magnetic resonance imaging (MRI) has been shown to be a very sensitive tool for identifying early sacroiliitis. In this study, the authors look at the ability of MRI to distinguish active and inactive disease in AS.

Eighteen patients with symptomatic AS who were participating in AS clinical trials underwent plain radiography and MRIs of their sacroiliac (SI) joints; the MRIs were performed both with and without gadolinium enhancement. In 17 of the 18 patients, MRI showed abnormalities at the SI joint. Ten of these had abnormal gadolinium enhancement and bone marrow edema, indicating active disease.

Findings on MRI were compared with clinical measurements of disease activity. Active disease on MRI correlated only with C-reactive protein level, and not with other indicators of disease activity, including the Bath AS Disease Activity Index, the Bath AS Functional Index, pain, physician global assessment, and patient global assessment. Fatty changes in subchondral bone marrow correlated with radiographical damage, but not with disease activity or disease duration.

The authors conclude that MRI, while a sensitive indicator of sacroiliitis in AS, is a poor surrogate for clinical measurements of disease activity. Given the link between fatty marrow changes on MRI and radiographical damage, they propose a continuum of MRI changes in AS, from bone...
marrow edema representing active inflammation to fatty marrow replacement with progressive disease.

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GENETICS

Haplotype analysis revealed no association between the PTPN22 gene and RA in a Japanese population

Single nucleotide polymorphisms in the protein tyrosine phosphatase non-receptor type 22 gene (PTPN22) have been associated with rheumatoid arthritis (RA) in populations of North European ancestry. This study suggests that PTPN22 is not associated with RA in a Japanese population; therefore, the gene might be associated with RA only in certain ethnic groups.

Susceptibility to rheumatoid arthritis (RA) has been estimated to have a genetic component of approximately 60%. Identification of the genes that are involved would contribute to the understanding of the disease’s pathogenesis. In the present article, the authors investigated the association between the protein tyrosine phosphatase non-receptor type 22 gene (PTPN22) and RA.

An association between RA and a single nucleotide polymorphism (SNP) within PTPN22, known as R620W, has been observed by different groups [1–3]. Furthermore, the SNP has been found to be associated with other autoimmune diseases such as type 1 diabetes, systemic lupus erythematosus, Graves’ disease, and juvenile idiopathic arthritis [2–3]. The association between R620W and autoimmune diseases, including the pathogenetic role of PTPN22, was validated repeatedly in populations of North European ancestry; however, the association could not be confirmed in Asian populations [4]. In addition to R620W, several other polymorphisms within PTPN22 have been identified. Therefore, in the present study, the authors attempted to find an association between PTPN22 and RA based on several SNPs within the gene in a large Japanese population.

DNA samples from patients with RA (n=1128) were selected for the study; 88% of the patients were positive for rheumatoid factor and 83% were female. DNA samples from 455 population-based controls were also used. All control subjects were matched for sex, ethnic origin, and geographical area. In addition to the well-studied functional SNP R620W, eight other SNPs were selected. Genotyping was carried out using a TaqMan 5’ nuclease assay. Fisher’s exact test was used to test for associations between RA and each of the SNPs. Haplotypes were constructed using the expectation-maximization algorithm. R620W did not exhibit a sufficient amount of polymorphism in either patients or controls to be included in the analysis. The frequency of each allele of the other eight SNPs was similar for the two groups, and haplotype analysis also suggested that PTPN22 was not associated with RA.

In conclusion, the data suggest that PTPN22 is not associated with RA in a Japanese population; therefore, the gene might be associated with RA only in certain ethnic groups.


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Rheumatoid arthritis association with the FCRL3 –169C polymorphism is restricted to PTPN22 1858T-homozygous individuals in a Canadian population

It is expected that the genetic factors mediating susceptibility to rheumatoid arthritis (RA) will be identified over the next 10 years, leading to the identification of pathways for new drugs to target and allowing better stratification of patients. The research presented in this article demonstrated that the association between FCRL3 and RA is mainly confined to patients who lack the PTPN22 gene variant that confers risk to this autoimmune inflammatory disease.

It has been suggested that a variant of FCRL3 (a gene encoding Fc receptor homologue 3) is associated with RA [1]. In the present study, 1187 Canadian patients with rheumatoid arthritis (RA) and 462 control subjects were genotyped for FCRL3 and PTPN22 (a gene encoding the Lyp protein tyrosine phosphatase).

Significant associations were found between RA and the FCRL3 genotype for both presence of the –169C allele (odds
observed in clinical practice remains to be seen. Genetic risk factors can affect different patients with RA. Conferred protection against this condition.

The relevance of this study is in showing that different genetic risk factors can affect different patients with RA. Whether this contributes to the genetic heterogeneity observed in clinical practice remains to be seen.

Audio-vestibular disturbance in patients with Behçet's disease
Choung YH, Cho MJ, Park K et al.

Inner ear involvement has been reported with Behçet's disease, but its frequency is not well described. This small, prospective series suggests that audio-vestibular abnormalities in Behçet's disease may be more common than previously recognized.

Behçet's disease is a systemic vasculitis and patients with the disease frequently present with recurrent oral and genital ulcers and uveitis. Inner ear involvement has been reported with Behçet's disease, although the frequency of this manifestation is not well described. In this investigation, the authors prospectively evaluated auditory and vestibular findings in a series of patients with Behçet's disease and compared them with those in control subjects.

Seventeen consecutive patients diagnosed with Behçet's disease were identified at a single institute (Ajou University School of Medicine, Suwon, Republic of Korea). Seventeen age- and sex-matched control patients were chosen for comparison, although the article does not report where these subjects were from. The cases included five males and 12 females, with a mean age of 41.2 years; those with a history of audio-vestibular disease or trauma were excluded. Subjects provided a full history of auditory and vestibular complaints and underwent a range of audiometry and vestibular function tests.

Seven of the patients reported auditory symptoms and 14 had vestibular symptoms. Abnormal test results were also common: ten subjects had abnormal audiograms, two had spontaneous nystagmus, and most had abnormalities in vestibular function testing. Overall, 16 of the 17 patients had abnormal audio-vestibular signs or symptoms, compared with none of the controls (the tests performed on control subjects were not described).

The results from this series suggest that audio-vestibular abnormalities may be more common in Behçet's disease than previously recognized, and that clinicians should take a careful audio-vestibular history and consider formal assessment in patients with symptoms. However, the lack of a clear description of the selection and testing of control subjects in this study limits the value of this series in identifying the true risk of audio-vestibular dysfunction in Behçet's disease.

Work disability in early rheumatoid arthritis: higher rates but better clinical status in Finland compared with the US
Chung CP, Sokka T, Arbogast PG et al.

Work disability can have major clinical and financial implications for people with rheumatoid arthritis (RA). This comparison of work disability rates in a cohort of patients with RA from Nashville, TN, USA, and a cohort from Jyväskylä, Finland, suggests that differences in social systems may partially explain variation in rates.

The authors of the present article were interested in comparing work disability in patients with early rheumatoid arthritis (RA) from two different social systems. Patients with early RA from Nashville, TN, USA (n=269, median disease duration at baseline 18 months), and patients from Jyväskylä, Finland (n=364, median disease duration at baseline 6 months), were <65 years old and were working at the time of their first RA symptoms. The article highlights several differences between the social systems of the US and Finland with regard to work disability.

Clinical and demographic data were evaluated at baseline, and follow-up data on physical function, pain, global status, and fatigue were obtained from self-report questionnaires.
Work disability was defined as continuous absence from work attributed to RA since the self-reported final working date. Cox proportional hazards regression was used to generate hazard ratios (HRs) for comparing the risk of work disability in the two cohorts.

Among the study population, 36.8% of the patients from Nashville and 73.6% of the patients from Jyväskylä had a disease duration of <1 year at baseline. A greater proportion of the US patients than the Finnish patients were positive for rheumatoid factor (RF), received aggressive treatment, and performed sedentary work. In both cohorts, a high risk of work disability was related to being female, having a lower educational level, being positive for RF, and having poorer scores for physical function, pain, and global status. The patients from Jyväskylä had a higher rate of work disability than those from Nashville (unadjusted HR 1.62, 95% confidence interval [CI] 1.07–2.46; HR adjusted for demographic and clinical parameters 2.58, 95% CI 1.44–4.59). Accordingly, the probability of continuing to work was significantly lower in the Jyväskylä cohort, compared with the Nashville cohort (p=0.02). However, the Finnish patients reported significantly lower levels of pain, fatigue, and global status at their last observation than the US patients (p<0.001).

The authors conclude that the risk of work disability in patients with RA might be predicted not only by demographic and clinical characteristics, but also by social system.

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**Predictors of post-partum damage accrual in systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (XXXVIII)**

Andrade RM, McGwin G Jr, Alarcon GS et al.


Systemic lupus erythematosus (SLE) is a disease that occurs predominantly in women of childbearing age. In this analysis of 63 women with SLE, strong predictors of post partum damage accrual were disease activity levels at pregnancy onset and the extent of damage prior to pregnancy.

The study authors analyzed the 63 women with at least one pregnancy after the diagnosis of systemic lupus erythematosus (SLE) from the LUMINA cohort of 544 women. The patients included in the analysis had a mean age of 27.6 years and a mean disease duration of 18.3 months.

Adverse pregnancy outcomes occurred in approximately three-quarters of the patients. The Systemic Lupus International Collaborating Clinics Damage Index score (a cumulative score of irreversible damage in 12 organs) increased from 0.19 before pregnancy to 0.60 after pregnancy. Unfortunately, the article does not provide information on damage accrual in similar patients who did not get pregnant.

The authors used a multivariate regression model of damage accrual, which accounted for a very impressive 57.8% of the variance. The strongest predictors were the extent of damage and disease activity before pregnancy; a less important predictor was disease duration.

This study provides sound supporting evidence for the clinical advice commonly given to patients with SLE that recommends planning pregnancy during a period of low disease activity.

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**Ethnicity and mortality from systemic lupus erythematosus in the US**

Krishnan E, Hubert HB.


Personalized medication is only possible when knowledge of prognostic factors is comprehensive. In this study, rates of mortality from systemic lupus erythematosus (SLE) were compared in African American and Caucasian people. The risk of mortality from SLE was 2–3 times higher in African American individuals, a difference that was disproportionately greater than the disparity in all-cause mortality.

The study authors analyzed data on mortality from the National Center for Health Statistics (Hyattsville, MD, USA) and data on hospitalization from the Nationwide Inpatient Sample, which is the largest US hospitalization database. In total, 22,751 deaths due to systemic lupus erythematosus (SLE) were reported between 1979 and 1998 from a total death count of 42.9 million.

All-cause mortality risk was higher in African American people than in Caucasian people, with an age-adjusted relative risk of 1.36 in men and 1.24 in women. The equivalent relative risks of mortality from SLE were much higher, with values of 2.40 in men and 3.91 in women. It is plausible that an SLE-specific biological factor – rather than just discrepancies in access to care and other socioeconomic factors – may explain this finding.

Analysis of temporal trends revealed an increase in the rate of mortality from SLE between 1979 and 1998 (p<0.001). This was probably due to increased attribution of deaths to SLE, given the improved diagnostic abilities over this time period.
The overall implication of the findings is that preventative interventions such as lifestyle changes (e.g., cessation of smoking and increased physical activity), control of hypertension and hyperlipidemia, and aggressive management of SLE, are warranted in African-American patients.

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**Peripheral neuropathy in primary Sjögren syndrome: a population-based study**

Reports on the frequency of extraglandular manifestations of Sjögren’s syndrome are often hampered by the “highly selected” samples of patients who are referred to specialists. This study investigated the involvement of neurological disorders in an “unselected” sample of patients with Sjögren’s syndrome. Approximately one-third of the patients had documented neuropathies, indicating that awareness of this complication is important in daily clinical practice.

Stavanger University Hospital (Stavanger, Norway) is the only hospital in an area with nearly 300,000 inhabitants. The medical record of every patient diagnosed with Sjögren’s syndrome (SS) at the hospital between 1980 and 2004 was reviewed. In addition, salivary gland biopsy samples from the hospital’s pathology department dated between 1990 and 2004 were examined.

Overall, 62 patients fulfilled criteria for primary SS and gave consent to be included in the study. Of these patients, 17 (27%) were diagnosed with peripheral neuropathy after clinical examination. Furthermore, nerve conduction studies yielded abnormal results in 34 (55%) of the patients. Based on both clinical examination and nerve conduction study criteria, eight patients had neuropathy, of whom three had sensorimotor neuropathy, three had motor neuropathy, and two had sensory neuropathy. Skin biopsies revealed that two of the 62 patients had reduced intra-epidermal nerve fiber densities that satisfied the definition of small-diameter nerve fiber neuropathy.

The underlying mechanism for the peripheral neuropathy seen in patients with SS is not yet clear. However, reports have suggested that this phenomenon may be related to perivascular infiltrates, an inflammatory process involving the vasa nervorum, or specific disease-inducing antibodies with reactivity against neurons, such as anti-Hu antibodies.

**MISCELLANEOUS**

**Signs of inflammation in both symptomatic and asymptomatic muscles from patients with polymyositis and dermatomyositis**


In this study, consecutive patients diagnosed with polymyositis or dermatomyositis underwent histopathological examination. Inflammatory infiltrates, muscle fiber expression of major histocompatibility complex class I and II antigens, and microvessel expression of interleukin-1α were observed to an equal degree in symptomatic and asymptomatic muscles. Therefore, subjective muscle symptoms appear to be independent of the degree of inflammation and may instead be related to other factors such as physical demands.

Polymyositis and dermatomyositis are chronic inflammatory muscle diseases involving proximal muscle weakness and inflammatory infiltrates in muscle tissue, mainly composed of T cells and macrophages. Other phenotypic changes include muscle fiber expression of major histocompatibility complex (MHC) class I and II antigens and microvessel expression of interleukin-1α (IL-1α).

In the present study, the expression of IL-1α and MHC class I and II antigens and the presence of T cells and macrophages were compared in symptomatic and asymptomatic muscles of eight patients with polymyositis, three patients with dermatomyositis, and six healthy controls, in order to test for a correlation between the observed phenotype and the clinical symptoms. Muscle weakness was confirmed by a reduced functional index, and muscle biopsy samples were analyzed for histopathological signs of myositis (inflammation, regenerating and degenerating muscle fibers, muscle fiber atrophy, and central nuclei). Furthermore, the muscle biopsy samples were analyzed by immunohistochemistry for the presence of T cells (identified by the expression of CD3) and macrophages (identified by the expression of CD163), and the expression of IL-1α and MHC class I and II antigens.

Histopathological changes were observed in both symptomatic and asymptomatic muscles of patients with polymyositis and those with dermatomyositis. These changes included the presence of inflammatory cells and regenerating and degenerating fibers. Specimens from healthy individuals did not show the changes. The biopsy specimens from both symptomatic and asymptomatic muscles had significantly higher numbers of CD3+ T cells and

**MISCELLANEOUS**
CD163+ macrophages than those from the controls. There was an increased number of IL-1α-positive capillaries in symptomatic and asymptomatic muscles compared with controls. MHC class I antigens were expressed to a similar degree in symptomatic and asymptomatic muscles (with only a few exceptions). Furthermore, in most cases there was also a strong similarity between the expression of MHC class II antigens in symptomatic and asymptomatic muscles. The healthy controls showed no muscle fiber expression of MHC class I or II antigens.

In conclusion, the degree of inflammation was not found to correspond to patients’ subjective muscle symptoms. Instead, other factors may be involved, such as physical demands, which would explain the greater reporting of symptoms in proximal muscles than distal muscles.

Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison


In this prospectively designed analysis, the investigators found that the incidence of thrombotic cardiovascular events in patients with arthritis receiving long-term therapy was similar in those treated with etoricoxib and those treated with diclofenac.

Cyclooxygenase 2 (COX-2) inhibitors have a comparable clinical efficacy to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) but are associated with a reduced risk of upper gastrointestinal complications. However, studies have demonstrated an increased risk of thrombotic cardiovascular events with COX-2 inhibitors compared with placebo [1–3]. Given that there is some evidence suggesting that traditional NSAIDs also increase cardiovascular risk [e.g. 4], studies clarifying relative risks of cardiovascular and gastrointestinal events among the different NSAID classes are important for guiding choice of long-term anti-inflammatory therapy.

The prospectively designed MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-Term) program pooled data from three long-term, randomized, double-blind trials with very similar characteristics: the MEDAL study, the EDGE (Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness) study, and the EDGE II study. The pooled data were from 34 700 patients aged ≥50 years – with either osteoarthritis (n=24 913) or rheumatoid arthritis (n=9787) – who received etoricoxib 60 mg/day or 90 mg/day or diclofenac 150 mg/day for a median duration of 18 months.

Thrombotic cardiovascular events occurred in 320 of the patients taking etoricoxib (1.24 per 100 patient-years) and in 323 patients receiving diclofenac (1.30 per 100 patient-years), resulting in a hazard ratio (HR) of 0.95 (95% confidence interval [CI] 0.81–1.11) for etoricoxib compared with diclofenac. Although a significantly lower rate of upper gastrointestinal clinical events (bleeding or symptomatic ulcers) occurred in the etoricoxib group compared with the diclofenac group (0.67 vs. 0.97 per 100 patient-years [HR 0.69, 95% CI 0.57–0.83]), the rates of “complicated upper gastrointestinal events” (i.e. perforation, obstruction, or major bleeding) were comparable for etoricoxib and diclofenac (0.30 and 0.32 per 100 patient-years, respectively). In addition, etoricoxib and diclofenac showed similar efficacy for treatment of arthritis.

In conclusion, patients with arthritis treated with etoricoxib and those given diclofenac had similar rates of thrombotic cardiovascular events. However, because the program did not include a placebo group, the absolute cardiovascular risks associated with etoricoxib and diclofenac cannot be determined. Moreover, the findings observed in this trial cannot necessarily be extrapolated to other COX-2 inhibitors or traditional NSAIDs.


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