Inflammatory arthropathies

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Abstract

There are a large number of potential causes of an inflammatory arthropathy, ranging from self-limiting viral infections to long-term systemic autoimmune diseases. The most common forms of inflammatory arthritis are rheumatoid arthritis and the spondyloarthropathies, a family of related inflammatory diseases including psoriatic arthritis and ankylosing spondylitis. These more common conditions form the basis of this review. There is growing evidence that in both rheumatoid arthritis and psoriatic arthritis, early initiation of treatment and tight control of disease activity improves outcomes. It is therefore important that these conditions are differentiated from other forms of arthritis early and accurately. This review focuses on the pathogenesis, clinical features, diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

Keywords ankylosing spondylitis; disease-modifying anti-rheumatoid drug; psoriatic arthritis; rheumatoid arthritis; spondyloarthritis

Introduction

It is estimated that over 10 million people in the UK suffer with arthritis of one form or another. These cases can be broadly divided into two main forms: non-inflammatory and inflammatory arthropathies. The most common non-inflammatory condition is osteoarthritis, but this group also includes a number of metabolic conditions. There are more than 100 potential causes of an inflammatory arthritis ranging from transient viral illnesses to chronic autoimmune conditions such as rheumatoid arthritis (RA). The management of these conditions can vary, making accurate diagnosis essential. This is achieved using a combination of clinical features and diagnostic tests. However, despite this high number of possible causes, most cases are attributable to a small number of more common conditions, particularly RA or a form of spondyloarthritis (SpA), within 1 year of presentation. As a result, these more common conditions will be the main focus of this review.

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Early and undifferentiated inflammatory arthritis

Patients with suspected inflammatory arthritis should be seen by a rheumatologist to make a diagnosis and, when appropriate, start treatment at the earliest opportunity. There are a large number of potential diagnoses to consider, some of which are listed in Table 1. Some conditions have the potential to be self-limiting and may require symptomatic treatment only, but these need to be differentiated from more serious or long-term diagnoses. Early intervention in inflammatory arthritis improves the prognosis and limits joint damage and subsequent disability. There is evidence that joint damage can begin early in the course of RA, with up to 25% of RA patients having evidence of bone erosion within 3 months of symptom onset.[1] Furthermore, a delay in treatment is associated with poorer outcomes, a reduced likelihood of achieving remission and an increased chance of developing resistance to targeted therapy later in the course of the disease. It is therefore postulated that in early disease there is a 'window of opportunity' in which early treatment can improve outcomes and increase the chance of sustained remission in patients with inflammatory arthritis.

Aggressive early treatment, with potentially toxic medications, has to be balanced against the fact that some cases of early inflammatory arthritis have the potential to resolve or go into remission without further intervention. Evidence suggests that in patients with early arthritis which does not yet meet the clinical diagnostic criteria for a specific condition (undifferentiated arthritis), approximately 30% will go into remission, 30% will be diagnosed with RA, 20% will receive an alternative diagnosis and 20% will remain undifferentiated.[1] Spontaneous remission in established RA is rare.

A clear history of the duration of symptoms and the pattern and number of joints involved can give important clues as to the type of arthritis (Table 1). A history of non-articular symptoms such as psoriasis, inflammatory bowel disease, recent infection or symptoms of connective tissue diseases, such as Raynaud's phenomenon, skin rashes, mouth ulcers or sicca symptoms, may aid diagnosis. Combining this with laboratory tests including serological tests for autoantibodies associated with RA (rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), or connective tissue disease (anti-nuclear antibodies (ANA), and imaging is essential in making an accurate diagnosis.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthropathy. Although it is the prototypical inflammatory arthritis, RA is in fact a complex multisystem autoimmune inflammatory disease. In most cases its articular features predominate, but it is important that RA is recognized as a syndrome which also has a number of systemic manifestations. It can lead to excess mortality, mostly through increased cardiovascular risk and an increased susceptibility to infection secondary to both to the disease itself and its management with immunosuppressive medication. Inadequately treated RA causes cartilage and bone damage and leads to progressive joint destruction, deformity and disability. However, over the last two decades the introduction of biologic and targeted synthetic therapies and 'treat to target' management strategies have revolutionized the management of

Examples of differential diagnoses in cases of inflammatory arthritis

Type of arthritis	Example	Clinical features
Viral	EBV, CMV, parvovirus	Acute polyarthritis/ arthralgia Associated symptoms of viral infection, e.g fever, rash.
Bacterial	Septic arthritis (e.g *Staphylococcus aureus*)	Usually monoarticular with knee most common joint affected. Can be oligo- or polyarticular in immunosuppressed.
	Gonococcal	Acute oligo- or polyarticular arthritis Associated with pustular skin rash and tenosynovitis.
Crystal arthritis	Gout (monosodium urate crystals)	Usually monarticular but can be polyarticular. First MTPJ commonly affected, but can affect any joint.
	Calcium pyrophosphate deposition disease (CPPD)/pseudogout	Mono- or oligoarticular. Larger joints such as wrist and knee more commonly affected.
Rheumatoid arthritis		Symmetrical polyarthritis. PIPJs, MCPJs, wrists and MTPJs most commonly affected.
Spondyloarthritis	Psoriatic arthritis	Associated with skin psoriasis Most commonly an asymmetrical polyarthritis. DIPJ involvement common
	Ankylosing spondylitis	Axial arthritis — affects SIJs and spine. Large joints may also be affected
	Reactive arthritis	Oligoarthritis associated with infection. Most commonly associated with GI infection or chlamydia
	Enteropathic arthritis	Polyarthritis or oligoarthritis associated with IBD
Connective tissue diseases	SLE	ANA-positive Polyarthritis.
	Scleroderma	
	Sjogren's syndrome	Associated with skin rashes, Raynaud's, serositis, sicca symptoms, sclerodactyly, myositis.
	Dermatomyositis/ polymyositis	

EBV, Epstein—Barr virus; CMV, cytomegalovirus; MTPJ, metatarsophalangeal Joint; PIPJ, proximal interphalangeal joint; MCPJ, metacarpophalangeal joint; DIPJ, distal interphalangeal joint; SIJ, sacroiliac joint; GI, gastrointestinal; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus; ANA, antinuclear antibody.

Table 1

RA and led to an improvement in outcomes for a majority of patients.

Epidemiology and risk factors

RA affects between 0.3 and 1% of the population in western countries,[2] making it one of the most common inflammatory diseases. The prevalence is higher in northern Europe than southern Europe. It affects all ethnic groups, although the prevalence can vary from 0.1% in black Africans to up to 5% in some North American Indians. It is two to three times more common in females than males. The onset of RA can occur at any age, with the peak incidence occurring within the fourth and fifth decades of life.

RA is a heterogeneous condition with myriad genetic and environmental factors involved in its development and evolution. It has long been established that there is a hereditable element to RA, with a relative risk of disease development in first- degree relatives of affected individuals of two or more. Studies in twins have suggested that the genetic contribution to RA is approximately 60%.[3] RA can be broadly divided into two subclasses based on the presence or absence of associated autoantibodies; ACPA and/or RF. Approximately 70% of patients are seropositive and 30% are seronegative. There are a number of genetic differences between seropositive and seronegative RA, which has led to some speculation that they should be classified as different conditions, although this remains controversial. In recent studies using genome-wide markers the genetic contribution to ACPA positive RA is again estimated to be up to 60%, with a lower estimate for ACPA negative RA of approximately 20%.[4]

Genome-wide association studies using single nucleotide polymorphisms (SNPs) have identified more than 100 loci associated with RA risk, dispersed widely across the genome, with an important concentration in genes associated with the immune system. The most influential genetic risk factor lies within the human leukocyte antigen (HLA) class II region encoding the HLA-DRB1 molecule with a conserved sequence of five amino acids, known as the shared epitope, conferring the largest genetic risk factor for RA. This strongly implicates peptide binding and antigen presentation in the pathogenesis of RA. The presence of the shared epitope is also a risk factor for more severe disease.

A number of lifestyle factors and environmental triggers have been associated with an increased risk of developing RA. Smoking is a well-recognized risk factor with an odds ratio for developing RA of 1.87 in current smokers and 1.76 in past smokers.[5] Obesity has also been strongly linked with both RA

development and an increased the risk of developing the condition before the age of 55. Inhalation of dusts such as silica and those produced in the manufacture of textiles have also been proposed as risk factors.[6]

Infectious triggers are speculated to be involved in the pathogenesis of RA. A number of viral infections including Epstein–Barr virus (EBV) and parvovirus have been proposed as triggers, but no clear link has ever been proven. There is also epidemiological evidence linking other types of microorganism to the development of RA. For example, the gut microbiome has also been implicated, with a number of studies identifying differences between the microbiome of RA patients and healthy controls.[7] Periodontal disease is also a recognized risk factor.[6] It has been hypothesized that a number of microorganisms associated with periodontal infection may be involved in the generation of ACPA with the subsequent risk of progression to RA.

Rheumatoid arthritis is a pathologically heterogeneous condition. In many cases autoantibodies are detectable in the sera of patients many years before they develop clinically identifiable arthritis. Therefore, it is speculated that RA begins with a high risk or susceptibility stage which is largely genetically based, and through the interaction of these genetic risks and environmental factors, evolves through a pre-clinical stage to established articular inflammation.[6]

Pathology

The pathological hallmark of RA is synovitis and its presence leads to the joint swelling and to pain, which is classical of the disease. In health, the synovium is a thin membrane consisting of one or two layers of fibroblast-like synoviocytes (FLS) and macrophages with a sub-lining of connective tissue, vessels and nerves. In RA, the synovium becomes inflamed and thickened due to the proliferation of resident FLS and macrophages, neoangiogenesis and an influx of inflammatory cells.[8] This thickened, proliferating synovium is known as pannus, which expands into the joint cavity and can invade and damage underlying cartilage. Cells within this synovium secrete inflammatory cytokines and chemokines, leading to the further recruitment, activation and retention of inflammatory cells within the joint. Tumour necrosis factor (TNF), interleukin (IL)-6, members of the IL-1 family, interferons and granulocyte macrophage colony-stimulating factor (GM-CSF), amongst others, are all elevated in the RA synovium.[9] The success of targeted drugs that inhibit both cytokines and autoreactive lymphocytes shows their importance in the pathogenesis of RA.

Clinical features

There is no one set of clinical features that definitively distinguishes RA from other types of inflammatory arthritis. As a result, RA is diagnosed using a combination of clinical features and laboratory tests. Most commonly, the onset of RA is insidious with symptoms of stiffness, fatigue and joint pain progressing to more overt joint swelling over time. However, a rapid onset of joint pain and swelling associated with systemic symptoms such as fever is also possible. A further subset of patients will suffer with palindromic rheumatism, which is typified by recurrent episodes of joint pain, swelling and systemic symptoms lasting hours to a few days at a time. Around 50% of patients with palindromic rheumatism ultimately progress to RA.

The wrists, proximal interphalangeal (PIP), metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints are most commonly affected in early disease, with other large joints becoming involved as the disease progresses. The distal interphalangeal (DIP) joints and thoraco-lumbar spine are very rarely involved. Signs and symptoms in these joints should point to an alternate diagnosis, with spondyloarthropathy and osteoarthritis being the most likely. Joint involvement in RA is classically polyarticular and symmetrical, but mono-articular and oligo-articular presentations in early disease are recognized. Joints affected by RA show signs of soft tissue swelling and warmth and may be erythematous. They are usually tender to palpation and will have a restricted range of movement.

Constitutional symptoms associated with RA include myalgia, fatigue, low appetite, weight loss and low-grade fever. Early morning stiffness is a classical feature, lasting anywhere from 30 minutes to several hours, often requiring a patient to rise early and not easing until after activity or a hot shower.

Untreated or suboptimally treated RA causes progressive joint damage, destruction and increasing disability. Invasion of pannus and degradation of extracellular matrix caused by the release of matrix metalloproteinases by inflammatory cells leads to loss of cartilage and secondary osteoarthritis. Bone erosion is a pathological hallmark of RA and can occur early in the disease. It is caused by the activity of osteoclasts enacting bone resorption at the pannus–bone interface. Periarticular osteoporosis and generalized osteopenia increase the risk of fracture, which may also contribute to joint damage. Inflammation, stretching and rupture of tendons and ligaments also contribute to deformity. Common deformities associated with RA include ulnar deviation of the fingers, volar subluxation of the MCPs and wrists, and boutonnière deformity (flexion of the PIP joint and hyperextension of the DIP joint), swan's neck (hyperextension of the PIP joint and flexion of the DIP joint) and fixed flexion deformities of the digits. Unlike the thoracolumbar spine, RA can affect the cervical spine. Erosion of the C2 odontoid peg and stretching or rupture of the transverse ligament of C1 can lead to atlantoaxial subluxation and consequent cervical myelopathy.

Extra-articular manifestations

Involvement of organs other than the joints tends to occur later in the course of the disease and is more likely in seropositive patients. Rheumatoid nodules are present in around a quarter of RA patients and are most commonly found in pressure areas such as the elbow. Nodules can also occasionally be found in the lungs, usually in smokers. Other forms of pulmonary disease include interstitial pneumonitis and pulmonary fibrosis. Serositis, particularly pleuritis and pericarditis associated with pleural and pericardial effusions respectively, are also seen in RA. These effusions are usually small and rarely require draining. Scleritis, episcleritis and rarely corneal melt are complications of rheumatoid arthritis in the eye. Vasculitis is an uncommon complication of RA which can lead to skin ulceration or peripheral neuropathy.

Investigations

Laboratory testing in patients with RA will usually show an elevation in inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), although there is a

recognized subset of patients who do not mount a significant inflammatory response despite active disease. A full blood count may show anaemia of chronic disease, whilst a thrombocytosis or leucocytosis associated with active inflammation may be present.

Rheumatoid factor and ACPA (anti-CCP) should be tested to both aid diagnosis and help to determine the prognosis of a patient's RA. The presence of autoantibody is associated with a more severe disease course.

Radiographs are helpful for both diagnosis of RA and monitoring disease progression. X-rays of the hands and feet are standard tests to look for erosive changes. Ultrasound scans of affected joints can also be used to confirm the presence of active synovitis.

Management of rheumatoid arthritis

The management of RA has evolved significantly over the last 20 years, with the focus of treatment now aimed at inducing and maintaining rapid remission. Corticosteroids given either orally or as intra-articular or intramuscular injections are quick and effective, but the high risks of side effects such as weight gain, diabetes and osteoporosis limit their use as a long-term strategy for RA management. They are particularly useful in early disease when combined with the initiation of methotrexate or when managing a disease flare.

Disease-modifying anti-rheumatoid drugs (DMARDS) are the mainstay of RA management. These can be either conventional synthetic DMARDs (csDMARD) or targeted DMARDs; a class which includes both biologic drugs (bDMARDs) and newer targeted synthetics (tsDMARDs) such as JAK inhibitors. CsDMARDs include methotrexate (MTX), sulfasalazine, hydroxychloroquine and leflunomide. Older csDMARDS such as gold and penicillamine are now rarely used. Methotrexate is the anchor drug used in the management of RA. It is efficacious in early disease and has a good long-term safety profile. Co-prescription of folic acid helps to reduce the risk of side effects. Methotrexate can be used in combination with other csDMARDs in patients with an inadequate response to monotherapy.

Currently, in the UK patients who have failed to respond to two csDMARDS (including MTX) are eligible to start a targeted therapy. There are a number of classes of biologic drugs; TNF inhibitors (TNFi) which include the TNF-receptor fusion protein etanercept, the monoclonal antibodies infliximab, adalimumab, golimumab and the PEGylated antibody fragment certolizumab pegol, the anti-IL-6 receptor monoclonal antibodies tocilizumab and sarilumab, the anti CD-20 monoclonal antibody rituximab and the T-cell co-stimulation inhibitor abatacept.[10] Recently the armamentarium has been further augmented by the introduction of the oral, small molecule, janus kinase (JAK) inhibitors tofacitinib and baricitinib. At present there are little data to suggest which targeted therapy is likely to be most effective in an individual patient and therefore considerations such as drug cost, patient preference and co-morbidity are important considerations.

Surgical intervention in RA may be required in advanced or refractory cases, including joint fusion, arthroplasty, and synovectomy. Consideration must be given to a patient's immunosuppressive medication when planning a surgical procedure. There are limited guidelines on this issue, but the British Society for Rheumatology recommends that anti-TNF drugs are stopped three to five times the half-life of the drug prior to surgery and, as a rule of thumb, this can be applied to most other biologic drugs. Rituximab is given as an intravenous infusion no more than once every 6 months and elective surgery should be delayed until at least 4 months post treatment. The risk of disease flare has to be balanced against the risk of infection and decisions on pausing RA treatment should always be taken in consultation with the treating rheumatologist.

Spondyloarthropathies

Spondyloarthritis (SpA) is a relatively recent term that brings together a group of conditions with shared clinical features and pathophysiology, including psoriatic arthritis (PsA), ankylosing spondylitis (AS), enteropathic (inflammatory bowel disease-associated) arthritis, reactive arthritis, and undifferentiated SpA.

SpA differs from RA in a number of ways. Clinically, SpA has a predilection for the axial skeleton, peripheral arthritis tends to be oligoarticular and asymmetrical, and additional features are seen, such as enthesitis, dactylitis, skin psoriasis, gastrointestinal inflammation and uveitis. SpA is also characterized by dual effects on bone, with erosions and osteoporosis occurring alongside pathological new bone formation. SpA conditions are autoantibody-negative and have major histocompatibility complex (MHC) class I associations. Recent disease models of SpA highlight the importance of non-adaptive immune mechanisms, including certain cytokine pathways, in disease pathogenesis, and place SpA towards the auto-inflammatory (as opposed to auto-immune) end of the immune-mediated disease spectrum.

In terms of pathophysiology, there has long been interest in the enthesis (the attachments of ligaments and tendons to bone) as the seat of disease initiation in SpA (in contrast to the synovium in RA), and enthesitis as a hallmark feature of these conditions. More recently, several lines of evidence have emerged to support a key pathogenic role of the IL23/IL17 cytokine axis. For example, HLA-B27-transgenic mouse models of SpA over-express IL23, gene studies in SpA patients have identified IL23R SNPs as a risk factor and clinical studies demonstrate raised IL23 levels in psoriasis and IBD. The recent finding of IL23-responsive, IL17-producing innate-like T cells resident in the mouse enthesis appears to provide a mechanistic link between the entheseal and IL23/IL17 theories, and a unified model of disease.[11]

Observations such as these have led to 'bench-to-bedside' development of biologic therapies targeting IL23 and IL17A, which are now licensed for use in SpA. Interestingly, neither has shown adequate efficacy in RA, providing compelling clinical evidence that different immunopathological processes underpin RA and SpA.

In clinical practice, whilst there is significant overlap between the conditions that make up the SpA family, there are also important distinctions, and it remains useful to consider them individually. The remainder of this section will focus on PsA and AS.

Psoriatic arthritis

PsA is an inflammatory arthritis associated with skin psoriasis. It is usually peripheral, but is heterogeneous in terms of the pattern of joint involvement and associated clinical features. Five phenotypes were originally described: oligoarticular, polyarticular

(which may resemble RA), DIP joint disease, axial disease, and arthritis mutilans. These days, PsA is commonly considered in terms of disease 'domains', which allows comprehensive assessment and can aid treatment selection: arthritis, skin disease, enthesitis, dactylitis, nail disease, and axial involvement.

Epidemiology and risk factors

PsA has a prevalence of around 0.3% in Caucasian populations and a male to female ratio of 1:1. PsA and skin psoriasis are less common in Black and Asian populations. The overall incidence appears to be increasing, which is likely in part related to increased recognition, but also to environmental factors such as the increasing prevalence of metabolic syndrome.

PsA is highly heritable, with a sibling relative risk of around five. Multiple low-impact genetic risk factors for PsA and skin psoriasis have been identified, including MHC class I alleles (HLA-Cw0602 and HLA-B27), and genes relating to TNF, IL12 and IL23 signalling. Interestingly, despite some shared genetic risk factors, PsA is much more heritable than skin psoriasis.

Skin psoriasis is an obvious risk factor for the development of PsA, particularly in patients with nail disease, scalp involvement and natal cleft involvement. Up to 40% of patients with skin psoriasis may have some form of PsA. Additional environmental associations include obesity and the metabolic syndrome, as well as psychosocial morbidity, but causality is difficult to establish. The relationship between PsA onset and smoking is controversial, with some studies showing an association, and others a protective effect.

Clinical features

PsA is usually distinguishable from RA in terms of its distribution and associated features. At onset, PsA is monoarticular, or oligoarticular and asymmetrical, in 70–80% of cases. It is more likely to become polyarticular over time. In the hands, a 'ray distribution' may be seen, where joints of the same digit are affected, in contrast to the typically symmetrical distribution ('rows') in RA. DIP joint involvement is a further distinguishing feature, and is present in up to 50% of patients with polyarticular involvement, and the predominant problem in 5%. The severity of PsA ranges from mild arthralgia to a destructive, erosive, highly disabling disease. Arthritis mutilans is the most severe form, characterized by telescoping of the digits, but is thankfully rare (<1% of cases).

Nail dystrophy is another characteristic feature of PsA, particularly in the context of DIP joint disease, and includes pitting, ridging and onycholysis. Enthesitis may manifest as Achilles tendonitis or plantar fasciitis, but subtler involvement elsewhere in the body is common and easily overlooked or mistaken for allodynia. Dactylitis, meaning inflammation of an entire finger or toe, is another clinical feature and results from a combination of joint synovitis, tenosynovitis and soft tissue swelling.

Axial disease, particularly sacroiliitis, is well recognized in PsA but is the predominant problem in only 5% of patients. However, up to 40% of patients may have some degree of axial involvement when careful screening takes place. Patients with axial involvement are more likely to be HLA-B27 positive.

The relationship between skin psoriasis and PsA is complex. There is generally no correlation between the two in disease activity or severity. Somewhat confusingly, a history of skin psoriasis is not required to make a diagnosis of PsA where the phenotype is otherwise convincing, and indeed PsA precedes skin psoriasis in up to 15% of cases (so-called 'psoriatic arthritis sine psoriasis'). That said, it is wise to examine carefully for psoriatic lesions, as they often occur in subtle or hidden places, such as the scalp, behind the ears, navel, natal cleft and external genitalia. Otherwise, a family history of skin psoriasis (or PsA) lends weight to the diagnosis.

In addition to skin and musculoskeletal manifestations, PsA is strongly associated with metabolic syndrome (obesity, hypertension, hyperlipidaemia, impaired glucose tolerance). Depression and anxiety are also common, although it remains unclear to what extent this link is biological (for example cytokine-mediated) or a product of other disease features (pain, rashes, obesity, etc.). Addressing modifiable cardiovascular risk factors and psychological health are therefore important aspects of holistic PsA care. Mortality in PsA appears to be comparable to the general population. However, there is a high degree of morbidity and a significant economic burden.

Investigations

As a rule, PsA is 'seronegative', meaning there are no autoantibodies or other specific blood tests. Negative RF and ACPA would therefore be expected. Genetic testing (e.g. for known HLA associations) is not usually undertaken in clinical practice. Non-specific findings may include raised inflammatory markers (with or without associated anaemia), particularly with active large joint or polyarticular involvement. However, inflammatory markers are generally lower than in RA and may be normal. Abnormal liver function tests may suggest underlying fatty liver disease, and uric acid is raised in around 20% of patients.

Radiographs can be useful for diagnosing and assessing damage in PsA. Compared with RA, PsA radiographs are typified by erosive change juxtaposed with new bone formation. Bone formation often occurs at entheseal sites and so is seen at joint margins or along bone shafts in the context of periostitis. The distribution of radiographic changes in PsA also differs from RA, mirroring the differences clinically. In severe, destructive PsA, 'pencil-in-cup' radiographic abnormalities can be seen, caused by osteolysis and whittling of the proximal portion of a phalanx (the 'pencil'), with erosions of the articulating surface of the adjacent bone (the 'cup'). Further imaging techniques, where available, also have a role; for example, ultrasound can detect subclinical synovitis and enthesitis, which can aid assessment of disease activity. Imaging features of axial disease will be discussed in the following section.

Management of psoriatic arthritis

As in RA, the main medical options are csDMARDs and tDMARDs. Intra-articular steroids may also have a role in monoarticular or oligoarticular disease, but can exacerbate skin psoriasis, hypertension, diabetes and weight gain.

Methotrexate and sulfasalazine are the most commonly used csDMARDs in PsA. Interestingly, there is minimal high-quality

evidence to support their use, including a recent randomized controlled trial comparing MTX to placebo, which failed to demonstrate superiority.[12] Nonetheless, they have been used for many years and remain first line; currently in the UK, patients can only qualify for further treatment after failure of these agents.

Several classes of tDMARDs are now available for PsA. Anti-TNF biologics were the first to be licensed and are still frequently used first-line. Newer licensed biologics include secukinumab and ixekizumab (targeting IL-17 A) and ustekinumab (targeting IL12/IL23). These are highly effective for skin psoriasis, but appear less effective than anti-TNF agents for joint disease. Newer still is tofacitinib, which has recently been approved for use in PsA. Finally, apremilast is a phosphodiesterase-4 inhibitor, also in tablet form, licensed only in PsA. Apremilast is less effective than other targeted therapies but has a lower risk of infection and does not require monitoring.

As in RA, it is not yet possible to select a treatment target based on an individual's disease (or cytokine) signature (so-called 'precision medicine'). Rather, the choice is shaped by clinical factors, including disease activity in each domain (IL17A and IL12/23 agents are particularly effective for skin but less so for arthritis, IL12/23 agents have limited impact on axial disease, apremilast may be suitable for mild disease), co-morbidities (concomitant inflammatory bowel disease (IBD) precludes the use of IL17A agents), infection risk (IL12/23 agents and apremilast are particularly low risk), and practical issues (preferred route and frequency of administration).

Outcomes in PsA are improved with early diagnosis and treatment, whilst delays are associated with higher incidence of erosive disease, joint deformity and disability. Whilst 'treat to target' has been standard practice in RA for years, evidence to support a similar approach in PsA has only recently emerged.[13] Treating to target is now recommended in international PsA guidelines.

Ankylosing spondylitis

Ankylosing spondylitis (AS) is characterized by axial inflammation and new bone formation. Spondylitis and sacroiliitis result in inflammatory back pain, and an important aspect of early clinical assessment is distinguishing this from the myriad other causes of chronic back pain (see below). Ankylosing spondylitis is defined by fusion of the sacroiliac and other spinal joints and can result in significant deformity and disability. However, modern imaging techniques, particularly MRI, can identify patients with axial inflammation in the absence of bony fusion (so called 'non-radiographic axial spondyloarthritis'). This has led to a re-conceptualization of disease, with AS seen as being on the severe end of a spectrum, and axial spondyloarthritis (axSpA) the unifying term.[14]

Epidemiology and risk factors

Ankylosing spondylitis is unusual amongst rheumatological conditions in having a strong male predominance (between 3:1 and 10:1). However, axSpA as a whole has a much more even sex distribution (non-radiographic axSpA has a female predominance). Prevalence is around 0.5–1% in Europe, the USA, and East Asia, and much lower in African populations.

Ankylosing spondylitis is highly heritable and has a strong, long-established MHC class I association with HLA-B27. Indeed, around 90% of AS patients are HLA-B27 positive. However, the relationship is complex and remains poorly understood. HLA-B27 is relatively common in the general population (8% in the UK), but only a small proportion develop disease. Additional genetic factors appear to modify the risk, illustrated by the fact that first-degree relatives have around 10 times greater risk of developing AS than HLA-B27 carriers in the general population. HLA-B27 appears to account for less than 50% of the overall genetic risk for AS, and genome-wide association studies have implicated numerous other genes.

The mechanism linking HLA-B27 to AS pathogenesis remains elusive. The traditional theory, that HLA-B27 presents an 'arthritogenic peptide' leading to breach of immunological tolerance, has never been corroborated. More recently, alternative theories, not involving antigen presentation, have been proposed that attempt to provide a mechanistic link between HLA-B27 and IL23/IL17.[15] For example, that HLA-B27 has a tendency to misfold in the endoplasmic reticulum, inducing IL23 over-production via the 'unfolded protein' cellular stress response. HLA-B27 can also form abnormal homodimers that may promote IL17 production by IL23-responsive CD4 T cells and NK cells.

In terms of environmental risk factors, there has been much recent interest in the gut microbiome relating to AS. This has been fuelled by laboratory findings, for example that HLA-B27 transgenic mice, when raised in germ-free conditions (meaning they have an absent gut microbiome), do not develop the usual spondyloarthritis-like features. It has also been suggested that HLA-B27 itself may modify the gut microbiome. Human studies are complex to conduct and interpret, but gut dysbiosis, including an abundance of prevotella copri, has been noted in AS patients.

Smoking is associated with radiographic progression in AS, so smoking cessation is strongly recommended.

Clinical features

Inflammatory back pain, a hallmark feature of AS, is chronic (>3 months) and insidious in onset, and tends to begin before the age of 40. It is characterized by prolonged morning stiffness (>30 min) and improvement with exercise. Nocturnal pain, causing wakening in the early hours, is also described. The location of pain depends to an extent on the part of the spine affected. Sacroiliitis is experienced as alternating deep buttock pain. Axial inflammation can also involve the costochondral joints; chest pain from costochondritis is very common in active AS, occurring in up to 50% of patients. Involvement of the hips is also common and can lead to accelerated osteoarthritis or even spontaneous joint fusion.

In terms of extra-axial manifestations, peripheral arthritis is relatively uncommon in AS, but where present tends to manifest as a lower limb mono- or oligoarthritis. Enthesitis, dactylitis and skin psoriasis can also occur. Acute anterior uveitis (iritis) is particularly common in AS, seen in around 25% of patients and is often recurrent. Symptoms include pain, photophobia and blurred vision, with redness and pupil irregularity seen on

examination. Prompt assessment and treatment (usually with topical corticosteroids) reduces the risk of permanent visual loss. Around 10% of AS patients have frank IBD and studies suggest that up to two thirds of patients have subclinical terminal ileitis. Cardiac involvement is also well documented in long-standing disease, including aortic root dilatation, aortic valve disease (regurgitation > stenosis) and conduction abnormalities (particularly atrioventricular block).

It is interesting to note that most of the anatomical sites affected in AS are subject to high mechanical stress; the axial skeleton and entheses are subject to loading, whilst the iris, gut lining and aortic valve are constantly exposed to forces as 'moving parts'. Mechanical stress appears fundamental to AS pathogenesis and may tie in with the physiological role of IL23 in providing protection at barrier sites, but this remains poorly understood.

Pathological new bone formation is a hallmark feature of AS. Ossification of intervertebral ligaments (syndesmophytes) can eventually lead to bridging and, along with sacroiliac joint fusion, results in ankylosis of the spine. Marked spinal deformity can occur, beginning with loss of lumbar lordosis, followed by exaggerated thoracic kyphosis, with cervical hyperextension in severe cases. Restriction of lumbar flexion, lateral spinal flexion and chest expansion can occur; lumbar flexion can be quantified using the modified Schober's test.

Bone loss occurs alongside aberrant bone formation and osteoporosis (including of the spine) is present in over half of patients. This results in a brittle vertebral column, predisposing to acute fracture. Fractures can result from hyperextension injuries or other minimal trauma and are most likely to occur transversely across the ossified disc (transdiscal), the weakest part of the column. At worst, spinal fractures can cause cord injury and paraplegia. Acute back or neck pain in AS should raise suspicion, even in the absence of trauma, and prompt urgent assessment by way of a CT scan. Chronic spinal fractures are also seen in AS, resulting in pseudo-arthroses (also known as Andersson lesions). These are most commonly thoracic, but can occur at any level, and may cause pain and tenderness, or be seen incidentally on imaging.

Investigations

As with PsA, there are no auto-antibodies in AS. Raised inflammatory markers and associated anaemia can again be seen. Testing for HLA-B27 can be useful in suspected inflammatory back pain where diagnostic uncertainty persists (e.g. lack of additional SpA features, no radiographic changes, etc.). However, for the reasons discussed above, HLA-B27 positivity is not diagnostic.

Pelvic or sacroiliac joint x-rays are an important test in suspected AS; true AS is, by definition, discernible radiographically as SIJ sclerosis, erosion or ankylosis. X-ray changes are not always clear-cut, and osteitis condensans, a benign finding that may or may not be associated with previous pregnancy, is a common differential. Radiographic changes elsewhere in the spine include squaring of the vertebrae (caused by erosions of the corners of vertebral bodies) and syndesmophytes; in advanced disease these can combine to give a 'bamboo spine' appearance.

X-rays are inadequate to detect early, 'pre-radiographic' AS, as X-ray changes reflect damage as a consequence of inflammation rather than inflammation itself. In addition, many cases of axial SpA never lead to radiographic changes, particularly in women (non-radiographic axial SpA). MRI has become a key investigation for inflammatory back pain, able to detect fatty infiltration and bone marrow oedema associated with inflammation (via T2-weighted sequences and short TI inversion recovery (STIR) sequence respectively) and confirm the presence of sacroiliitis or spondylitis.

Management of ankylosing spondylitis

Physiotherapy is the most important non-pharmacological intervention and is of particular importance in AS. Regular spinal exercises improve pain and stiffness and help maintain spinal mobility in the longer term.

NSAIDs have an important role in AS treatment. Inflammatory back pain responds well to NSAIDs, to the extent that a lack of response raises diagnostic doubt. Whilst NSAIDs in RA and PsA are used for pain relief only, they may have a disease-modifying role in AS; there is some observational data to suggest they delay radiographic progression. They are the first-line medical treatment, and in the UK a trial of at least two NSAIDs over 3 months is needed before further treatment can be considered.

Conventional synthetic DMARDs, such as MTX and sulfasalazine, are ineffective for treating axial inflammation and are not part of accepted treatment algorithms.

Anti-TNF biologics are highly effective in AS and have been in use for almost 20 years. Secukinumab (anti-IL17A) is also now licensed. Interestingly, agents targeting IL12/23 (ustekinumab) are relatively ineffective for AS and axial inflammation generally, despite the proposed key role of IL23 in pathogenesis. Reasons for this are unclear and a number of theories have been proposed, including poor penetration deep within the spine to sites of active disease. JAK inhibitors are under study in AS but are not yet licensed for use in clinical practice.

Whilst anti-TNF agents are highly effective at relieving inflammatory symptoms and resolving inflammatory lesions on MRI, there is controversy regarding to what extent they prevent or delay development of ankylosis. Recent data suggest a possible benefit when commenced early and continued long-term, but the lack of clear inhibition of radiographic progression raises the possibility that new bone formation is uncoupled from inflammation (or at least TNF-driven inflammation). This may be due to separate osteoproliferative signalling pathways that are not inhibited by anti-TNF agents, for example involving IL-22, and is an active area of research.

There are a number of scenarios where surgical intervention may be needed in AS. As discussed, vertebral fractures are well-recognised and may need urgent stabilisation. Corrective osteotomies may also be indicated in advanced spinal deformity, to improve pain, function and quality of life. Hip osteoarthritis can be severe and debilitating in AS, preventing hip flexion and forward bending, and hip arthroplasty outcomes (particularly when performed early) are generally good.

Conclusion

There are a large number of potential causes of an inflammatory arthropathy. Early diagnosis and initiation of treatment has the

potential to limit joint damage and reduce morbidity. Recognizing patterns of joint involvement and associated systemic features, and combining this with test results, can help to identify those patients who require early initiation of treatment. Rheumatoid arthritis and spondyloarthropathies are the most common forms of chronic inflammatory arthropathy. The advent of targeted therapies for these conditions has revolutionized their management over recent years. ◆

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