Rheumatoid Arthritis and Spondyloarthritis

8

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8.1 Introduction

Recent years have seen extraordinary growth in our knowledge and understanding of the pathogenesis of inflammatory arthritis as reflected in the development of new therapies and changing clinical practice. This chapter will review the most common forms of inflammatory arthritis, including rheumatoid arthritis, the axial spondyloarthritides (radiographic axial spondyloarthritis (r-axSpA) and the non-radiographic axial spondyloarthritis (nr-axSpA)) as well as psoriatic arthritis (PsA) to explore their epidemiology, pathogenesis, clinical features and treatment.

8.2 Rheumatoid Arthritis

8.2.1 Historical Perspective

Rheumatoid arthritis (RA) has been recognised in Europe since the seventeenth century, with Sydenham publishing the first case report in 1676. The artwork of the Dutch painter Peter Paul Rubens (1577–1640) is thought by some to show evidence of hand deformities that can occur in RA (Appelboom et al. 1981). Interestingly, the typical erosive changes of RA have not been found within the European fossil record, yet the characteristic joint damage found with gout, osteoarthritis and ankylosing spondylitis has been well documented

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(Aceves-Avila et al. 1998). Similar evaluation of skeletal remains from indigenous North Americans has shown these characteristic changes. In these areas, prevalence of RA remains remarkably high at around 5 % (Rothschild et al. 1988). This has led to speculation that perhaps RA was brought from the New World back to the Old World by returning explorers. Currently, there is no direct evidence supporting this.

8.2.2 Epidemiology

Rheumatoid arthritis has a worldwide distribution affecting all ethnic groups, and although all ages can be affected, the peak incidence is between the 4th and 6th decades with females being affected 2–4 times more commonly than males. The gender ratio becomes less pronounced with increasing age. Prevalence varies considerably, but published work suggests that ~0.5–1 % of European and North American adults are affected, with rates being lower in Southern Europe than Northern Europe and highest in native North Americans (Alamanos et al. 2006).

Several authors have suggested that RA appears to be becoming less common and less severe, and there is evidence that the incidence of extra-articular features is declining (Turesson and Matteson 2009). The change in incidence appears to have begun before the advent of aggressive disease management strategies and remains unexplained.

8.2.3 Pathogenesis

Insights into the pathogenesis of RA have been gained through the study of affected tissues, genetic studies and modern molecular approaches. Nevertheless, despite the growth in our understanding of the mechanisms underlying RA, it is not yet possible to unite the different elements into a comprehensive explanation of the heterogeneous phenotype.

As we shall see, RA has features of both T-cell activation with the formation of rheumatoid nodules and also B-cell activation with autoantibody production. Indeed, microscopic examination of synovial tissue from inflamed joints shows evidence of a dense but non-specific infiltration of inflammatory cells including neutrophils, B-cells, T-cells, macrophages and mast cells.

The inflammatory response is coordinated by a complex cytokine network with macrophages being the key secretors of pro-inflammatory cytokines in the inflamed rheumatoid synovium. It is now known that the cellular basis of the inflammatory response changes as the disease progresses with T-cells playing an important role in the early stages of disease (Raza et al. 2005).

Inflammation within the synovium results in the formation of a destructive pannus that may lead to the erosion of bone and consequent deformity and functional impairment. Recent work has suggested that bone oedema on MRI scan can predict future erosion, suggesting that the process of erosion may begin within the bone.

8.2.4 Cellular and Molecular Mechanisms

The first clues to the autoimmune nature of RA came from the discovery of a "rheumatoid factor" in the serum of affected patients by Waaler in 1938. Subsequently rediscovered by Rose in 1948, it was to be another 9 years until this rheumatoid factor was characterised as an antibody that binds to the Fc portion of immunoglobulin (Franklin et al. 1957). Whilst rheumatoid factor is most commonly IgM directed against the Fc portion of IgG, it can also exist in IgA and IgG subtypes. A proposed mechanism of action of rheumatoid factor was put forward in 1973 by Zvaifler in which immune complexes were formed that subsequently fixed complement and released chemoattractant factors to recruit neutrophils and other inflammatory cells to the synovium (Zvaifler 1973). Whilst there is considerable evidence to support this hypothesis, one of the key arguments against it is that rheumatoid factors are found in up to 15 % of the healthy older population and in those with other autoimmune diseases, infection and malignancy without joint involvement.

Subsequently, numerous other autoantibodies have been detected in the sera of patients with rheumatoid arthritis including anti-perinuclear factor and anti-keratin antibodies. Characterisation of these antibodies revealed that they were binding to citrullinated filaggrin (Girbal-Neuhauser et al. 1999), with citrullinated epitopes on fibrinogen and vimentin also acting as targets. Citrullination is a post-translational modification of the amino acid arginine, and the process is thought to have a natural role in apoptosis. The modification is carried out by the enzyme peptidyl arginine deiminase (PAD) in the presence of relatively high calcium concentrations. Commercial assays are now available for anti-citrullinated peptide antibodies (ACPA) which are found in 60–70 % of people with RA and rarely in other diseases. These antibodies can be present for up to two decades before symptoms develop (Jørgensen et al. 2008). It has been shown that ACPAs can directly initiate the differentiation of bone-resorbing osteoclasts, suggesting an independent effect of these antibodies in initiating skeletal damage (Harre et al. 2012). Moreover, IgG sialylation was reported to be a main regulator for the pro-osteoclastogenic potential of immune complexes as only non-sialylated immune complexes stimulated osteoclastogenesis in patients with RA. Current data indicate that RA patients with low IgG and low ACPA sialylation suffer from poorer bone microstructure as compared to those with a high-sialylation status (Harre et al. 2015). Therefore, bone resorption occurs also in the absence of inflammation, as has also been shown in healthy, ACPA-positive individuals with local bone loss (Kleyer et al. 2014). Moreover, systemic bone loss and secondary osteoporosis in RA seem to be triggered by ACPAs (Kocijan et al. 2014b). In addition, it has been shown that in patients with ACPA positivity, tapering and even stopping of antirheumatic treatment are associated with a higher risk for relapse (Haschka et al. 2016).

The abundance of Th1 cytokines such as IFN-γ and the relative lack of the Th2 cytokines IL-4, IL-5 and IL-12 support the hypothesis that RA is primarily a Th1 disease. However, in recent years, our understanding has changed with the discovery of a new subclass of regulatory T-cell that produces IL-17, the Th17-cell. Production

of IL-17 by these cells is driven by IL-23 which shares a common subunit with IL-12. Increased concentrations of IL-17 and IL-23 are found in the sera of patients with RA compared to controls with osteoarthritis, thereby supporting their role in the disease. In addition, mice deficient in IL-23 are resistant to developing arthritis in the collagen-induced arthritis model. The Th17-cells produce TNF-α, IL-6, IL-17, IL-22, and GM-CSF, cytokines known to be important in the inflammatory response. IL-17 is an important stimulator of further cytokine production including IL-1β, IL-6, IL-23, IL-8, GM-CSF, G-CSF, VEGF, and COX-2, thereby amplifying the immune response (Furuzawa-Carballeda et al. 2007; Lundy et al. 2007). IL-17 and Th17 cells have therefore become an important area of research and offer new therapeutic targets. The role of the activated macrophage in the synovium of affected joints is crucial to the maintenance of chronic inflammation. In addition to interaction with T-cells and fibroblasts, the macrophage is a potent effector cell that produces pro-inflammatory cytokines, expresses toll-like receptors (TLRs) and is involved in antigen processing and presentation. They also have phagocytic ability and are involved in tissue remodelling. Interestingly, the macrophage also responds to oestrogen concentrations, such that a high concentration (as in pregnancy) inhibits IL-1 secretion (Cutolo and Lahita 2005). This may be responsible in part for the improvement many women experience during their pregnancies.

The presence of autoantibodies, together with the formation of germinal centre-like structures in the synovium of affected joints and the good therapeutic response to B-cell depletion, suggests that B-cell dysfunction is also important in pathogenesis. B-cells have several roles in both humoral and innate arms of the immune system including antigen presentation and antibody and cytokine production. The link between humoral and innate responses is evidenced by the expression of TLRs on B-cells. These receptors can bind to hypomethylated CpG sequences in bacterial or mitochondrial DNA, single-stranded RNA or bacterial cell wall components, and it has been shown that mitochondrial DNA from apoptotic synovial cells can stimulate potentially autoreactive B-cells through this mechanism (Leadbetter et al. 2002).

Central to the development of autoimmunity is the breakdown of tolerance. Given that the majority of patients develop RA at an age when thymic function has severely declined or ceased entirely, the defect is more likely to be with peripheral tolerance rather than central tolerance. The precipitating event in RA is not yet known, but the T-cell repertoire in those with RA is altered in a number of respects from those without RA, including evidence of early senescence as evidenced by reduced telomere lengths (Colmegna et al. 2008). In addition, the T-cell repertoire appears to be reduced by a factor of 10 in those with RA compared to controls without RA (Wagner et al. 1998). Since the proliferation of naive T-cells is dependent on antigenic stimulation, over time, this will lead to the development of a peripheral T-cell repertoire with an increasing affinity for self. Thus, it is hypothesised that defective thymic selection coupled with peripheral selection over time predisposes the susceptible individual to the development of autoimmunity.

8.2.5 Genetics

Concordance rates in monozygotic twins indicate that approximately 50 % of the variation in prevalence of RA is genetic and that 30 % of this is attributable to the HLA-DR locus. Experiments first performed in 1969 identified a region on chromosome 6, now known to code genes within the major histocompatibility complex (MHC). Further work has mapped the linked region precisely to the third hypervariable region of the HLA-DRβ chain (Nepom 1989). The precise amino acid sequence between positions 70 and 74 appears to be particularly important as variations in the sequence both increase and decrease the risk of ACPA-positive RA. The amino acid sequence DERAA appears in ~30 % of healthy controls but in only 15 % of patients with RA and tends to be associated with less erosive disease when present, whereas the sequence QKRAA, QRAAA or RRRAA appears to increase the risk of ACPA-positive RA. Thus, it appears that the amino acids in positions 70 and 71 modulate the T-cell response such that the amino acids arginine (R), glutamine (Q) or leucine (K) increase the risk and alanine (A) or glutamic acid (E) is protective (van der Helm-van Mil et al. 2005). Work continues to establish exactly how these differences confer variable risk. This sequence is common to several HLA-DR alleles including DR*0101, DR*0102, DR*0401, DR*0404, DR*0405, DR*0408, DR*1001 and DR*1402 and has been termed the "shared epitope" by Gregersen et al. (1987). Individuals who are heterozygous for one of these alleles tend to have more severe, erosive disease. The effect is further intensified by homozygosity (Weyand et al. 1992).

Further work on the HLA region has found an association between the HLA-DR3 locus and ACPA-negative RA (van der Helm-van Mil et al. 2007). The precise mechanism by which genes at this locus influence disease is not known, although it is conceivable that DR3 polymorphisms could be predisposed to production of an as yet unidentified antibody.

Genetic factors independent of the HLA region have also been identified. The C>T single nucleotide polymorphism at position 1858, causing a missense mutation in the protein tyrosine phosphatase (PTPN22) gene, has been linked to ACPA-positive RA (Wesoly et al. 2005). The polymorphism has been validated in Canadian, North American and European populations, but does not appear to exist in Asians. Protein tyrosine phosphatase exerts a negative feedback regulation in T-cell receptor signalling; it binds to the regulatory kinase, Csk, and this complex is responsible for the dephosphorylation of the Lck protein at position 394 and its phosphorylation at position 505, thereby terminating the T-cell receptor signal. The C>T 1858 polymorphism appears to directly modify the phosphorylase activity or affect the binding of PTPN22 to Csk (Cloutier and Veillette 1999). Interestingly, the polymorphism has also been found in a number of other autoimmune diseases including type I diabetes, Graves' disease, SLE, JIA and vitiligo and appears to be a gain-of-function mutation that is hypothesised to impair thymic selection of autoreactive T-cells (Bottini et al. 2006). The genetic factors above are neither necessary nor sufficient for the development of RA; however, they do indicate that these pathways are important for disease susceptibility in individual patients.

8.2.6 Environment

Genetic factors alone are unable to account for the susceptibility to RA, and attention has focussed on environmental triggers for the disease. Pathogens including Epstein-Barr virus, Parvovirus B19 and mycobacteria have been investigated. To date, pathogen-derived antigens have not been discovered and evidence for molecular mimicry is lacking.

The most consistent environmental factor is cigarette smoking, wherein there appears to be a relationship between the number of pack-years of cigarettes consumed and the risk of developing RA, which can be as much as 21-fold above non-smokers (Klareskog et al. 2006, 2007). Importantly, smoking increases the risk for ACPA-positive RA, but not ACPA-negative RA, and the risk is further increased in those who possess the shared epitope. There are two hypotheses that might explain the link between smoking and ACPA-positive RA. Firstly, the detection of citrullinated peptide in the alveolar fluid of smokers has led to the hypothesis that smoking induces apoptosis in the lung, generating citrullinated peptides that are then recognised more strongly by those with the shared epitope who then develop RA. Secondly, smoking is known to increase the levels of tetrachlorodibenzo-P-dioxin (TCDD) which has been shown to upregulate IL1β, IL-6 and IL-8 production through binding to the aryl hydrocarbon receptor. Recently, work on the pharmacokinetics of methotrexate, the drug used most commonly to treat RA, has shown that smoking also reduces intracellular methotrexate polyglutamate levels, which may account, in part, for the unfavourable outcome in smokers (Stamp et al. 2009).

Other environmental factors that have received attention include coffee and alcohol consumption, periodontitis, exposure to mineral oils and body mass index; however, these factors are not as consistent as cigarette smoking and should be interpreted with caution. Additionally, pregnancy does appear to be a risk factor in as many as 12 % of females developing RA do so within 1 year after pregnancy.

Besides the risk of development of RA, the presence of autoantibodies, environmental and genetic factors such as smoking, HLA-DRB genotype and low socioeconomic status has been identified as poor prognostic factors in RA (Manfredsdottir et al. 2006; Kaltenhauser et al. 2007; Harrison et al. 2005; Hetland et al. 2009; Sanmartí et al. 2007).

8.2.7 Mechanisms of Bone Erosion

In RA there appears to be a coupling between the processes of inflammation and bone erosion. TNF-α is capable of binding to two receptors, designated TNFR1 (or p55) and TNFR2 (or p75); the former appears to have greater activity as it is directly coupled to a death domain that can induce apoptosis. Both receptors for TNF-α, but mostly TNFR1, are found on osteoclast precursors, osteoclasts as well as on osteoblasts. These cells are also capable of secreting TNF-α in response to external stimulation.

The osteoclast is the key cell type involved in the destruction of bone within the inflamed rheumatoid joint. Osteoclast differentiation required the cytokines macrophage colony-stimulating factor (M-CSF) and the receptor activator of NF-kB (RANKL). M-CSF promotes proliferation and survival of the monocyte lineage through activation of a tyrosine kinase (cFms) and RANKL through binding to its receptor. RANK leads to activation of the transcriptions factors NFATc1, AP-1 and NF-kB required for osteoclast differentiation. Since RANKL is part of the TNF superfamily and RANK shares many of the TNF-α signalling properties, it is conceivable that the elevated levels of TNF-α found in inflammatory arthritis contribute to the increased osteoclast differentiation (Abu-Amer et al. 2000; Kobayashi et al. 2000). This is strengthened by the finding that the in vitro differentiation of osteoclast precursors lacking RANK could be driven by TNF-α and TGF-β (Kim et al. 2005). It would appear, however, that in vivo osteoclast differentiation required IL-1 as TNF-α alone is unable to activate the transcription factor TRAF-6, a necessary condition for the formation of the actin ring structure required for bone resorption (Nakamura et al. 2002). The central role of TNF-α in the regulation of bone metabolism is presented in Fig. 8.1.

In RA, the source of RANKL is mainly from stromal cells including fibroblasts and osteoblasts, stimulated in turn by the action of the inflammatory cytokines, IL-1, IL-6, TNF-α and IL-17. In addition, RANKL is produced by CD4+ regulatory T-cells recruited to the inflamed synovium. The effects of these cytokines on osteoclast progenitors are amplified by upregulation of RANK through the direct action of IL-1β and TNF-α on the progenitor cells.

The process of erosion results as a consequence of both increased bone resorption and reduced bone healing. This suggests alterations in osteoblast function, and indeed, TNF-α is a potent inhibitor of osteoblastogenesis through inhibition of the transcription factors Runx2 and Osterix (Lu et al. 2006). Additionally, TNF-α inhibits Wnt signalling, a major pathway regulating osteoblast differentiation (Baron et al. 2006). Members of the Wnt family of cytokines bind to complex membrane-bound receptors incorporating the Frizzled protein and LRP5 and 6. TNF-α is able to interfere with this process at multiple levels by inducing *secretable* Frizzled-related proteins and by production of Dickkopf-1 and sclerostin that interfere with binding of LRP5 and 6 to the Frizzled receptor (Diarra et al. 2007). Increased serum levels of Dickkopf-1 and an association to bone erosions and osteoporosis were reported in patients with RA (Rossini et al. 2015).

In summary, the effects of systemic inflammation are to enhance bone resorption through osteoclast differentiation and activation and to impair bone healing by inhibition of osteoblast differentiation. Our increased understanding of the molecular mechanisms of bone erosion and repair has opened up novel therapeutic targets to prevent bone erosion in RA. The results of a 12-month study of denosumab, a monoclonal antibody directed against RANKL in RA, have shown reduced evidence of erosive damage on MRI scan as early as 6 months after treatment (Cohen et al. 2008). Consistent with its mechanism of action, this antibody has no effect on measures of disease activity in RA. Similar effects were shown for the sclerostin antibody, which did not affect joint swelling or synovitis but blocked and reversed

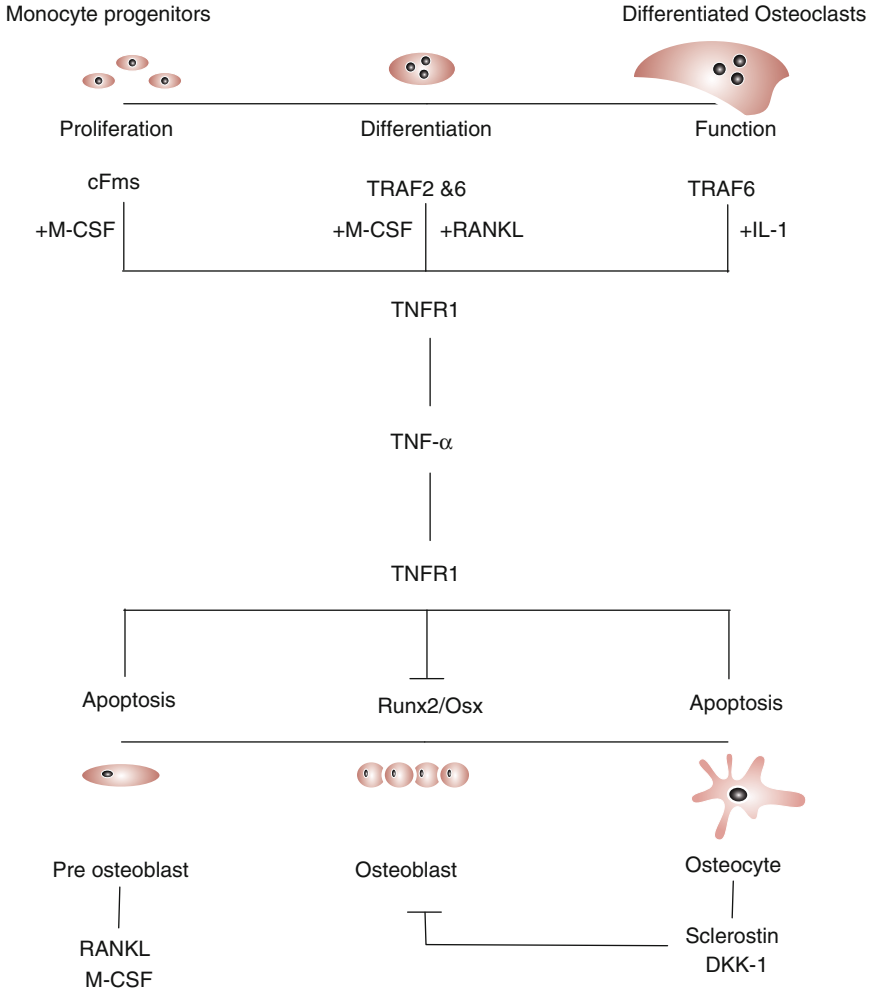

Fig. 8.1 The central role of TNF-α in bone metabolism (Adapted from David and Schett (2010))

periarticular bone loss in patients with RA. The sclerostin antibody arrested the progression of bone erosions and showed positive effects on the articular cartilage (Chen et al. 2013).

8.2.8 Diagnosis and Presentation

The new criteria set for the classification of RA were introduced in 2010 by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). Therefore, the diagnosis of RA can be made in the (i) presence of synovitis in at least one joint, (ii) the absence of alternative diagnosis and

Table 8.1 The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA

	Criterion	Score
A	Joint involvement	
	1 large joint	0
	2–10 large joints	1
	1–3 small joints (with or without large joint involvement)	2
	4–10 small joints (with or without large joint involvement)	3
	>10 joints (including at least 1 small joint)	5
B	Serology	
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
C	Acute phase reactants	
	Normal CRP and ESR	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms	
	<6 weeks	0
	>6 weeks	1

The new criteria should not be applied if the symptoms are explained by another disease; joint involvement includes either tenderness or swelling and can include imaging assessment. RA is defined as a score of > 6/10

(iii) a score of 6 or more points out of the following items: number and site of affected joints, serologic parameters, elevation of acute-phase proteins and duration of symptoms (Aletaha et al. 2010). The new classification criteria especially focus on early diagnosis of disease to prevent longstanding effects related to RA (see Table 8.1). These replace the 1987 criteria which had poor sensitivity to early disease.

Presentation may be preceded by a period of non-specific malaise with widespread aches and pains and fatigue. Symptoms can evolve slowly or start suddenly and can affect all joints from the beginning or spread to affect different joints as disease progresses. Classically, the patient will describe symptoms with an "inflammatory rhythm" where their symptoms are worst early in the mornings or overnight and improve during the course of the day.

Disease is not confined solely to the joints, and there are well-described extra-articular features (Table 8.2). The incidence of cardiovascular disease and lymphoma is increased in RA. Indeed, the major cause of premature mortality in RA is cardiovascular disease. The incidence of extra-articular features appears to be falling, possibly as a consequence of earlier diagnosis and more aggressive initial management; however, the decline appears to have begun before these management changes were well established.

Table 8.2 Extra-articular manifestations of RA

Organ system	Extra-articular manifestation
Eye	Scleritis, episcleritis and scleromalacia perforans, keratoconjunctivits sicca
Skin	Rheumatoid nodules, vasculitis, pyoderma gangrenosum, panniculitis
Lung	Pulmonary fibrosis, rheumatoid nodules, pleural effusion
Haematological	Anaemia, Felty syndrome
Nervous system	Vasculitis, peripheral neuropathy, atlanto-axial subluxation
Kidney	Amyloidosis
Cardiovascular	Accelerated atherosclerosis, pericarditis

8.2.9 Treatment of RA

Based on the treat-to-target (T2T) recommendations, the treatment aim is defined as remission with low disease activity as an acceptable alternative goal. The long-term health-related quality of life, the prevention of structural damage and the normalisation of function and social participation were defined as primary goals in patients with rheumatoid arthritis (Smolen et al. 2010). Should the patient's current therapy prove insufficient, therapeutic adaptation to reach treatment goals is recommended after 3–6 months. Follow-up examinations should include assessment of disease activity and joint counts (Smolen et al. 2016).

Pharmacological management of RA can be thought of in terms of agents to relieve symptoms and agents to suppress the underlying disease. Many patients benefit from the use of non-steroidal anti-inflammatory drugs (NSAIDs) which can be helpful for relief of pain and stiffness. They are however associated with potential side effects of gastric irritation, nephrotoxicity and increased cardiovascular risk making their long-term use undesirable. Similarly, simple pain killers such a paracetamol alone or in combination with weak opioids can be useful for some patients. However, these medications do not have any effects on the progression of erosive disease. Therefore, a conventional disease-modifying antirheumatic drug (DMARD) therapy is recommended in treatment of naive patients with early and established RA. If disease activity remains high despite conventional DMARD therapy, then combination conventional DMARD therapy or a biological treatment is recommended. In case of flare, short-term glucocorticoid therapy could be added (Singh et al. 2015). Conventional DMARDs and biological therapy are shown in Table 8.3.

Intervention with early combination DMARD therapy has been shown to have beneficial effects on disease progression independent of treatment in later years, suggesting that there is a "window of opportunity" in which the disease process can be altered (Boers et al. 1997; Möttönen et al. 1999). In addition, it has been calculated that the risk of undertreatment is 5–6 times the risk of overtreatment if all patients are treated aggressively from the outset, providing justification for an aggressive approach in early RA (de Vries-Bouwstra et al. 2006). Recommendations from EULAR have advised that the combined efficacy of methotrexate (MTX) and

Table 8.3 Disease-modifying anti-rheumatic drugs currently available for the management of RA

	Typical dosing	Proposed mechanism of action	Common side effects
Conventional DMARDs			
Methotrexate (MTX)	o, s/c max 30 mg/week	Inhibition of folate metabolism Inhibition of Adenosine release	Myelotoxicity, hepatotoxicity
Sulphasalazine (SSZ)	o, 2000–3000 mg daily	Uncertain	Myelotoxicity, hepatotoxicity
Hydroxychloroquine (HCQ)	o, 200–400 mg daily	Alteration of lysosomal pH	Ocular toxicity
Azathioprine (AZA)	o, 150–200 mg daily	Anti-metabolite	Myelotoxicity, hepatotoxicity
Gold (IMG)	im, 50 mg 3–4 weeks	Uncertain	Myelotoxicity, nephrotoxicity
Cyclosporine A (CSA)	o, 200–400 mg daily	Inhibition of IL-2 signal transduction	Nephrotoxicity
Leflunomide (LEF)	o, 10–20 mg daily	Inhibition of pyrimidine synthesis	Myelotoxicity, hepatotoxicity, gastrointestinal upset
Biological DMARDs			
Etanercept	s/c, 50 mg weekly	Soluble TNF receptor	
Adalimumab	s/c, 40 mg every 2 weeks	Humanised anti-TNF antibody	Infection TB reactivation, drug-induced lupus
Infliximab	iv, 3 mg/kg 0, 2, 6 then 8 weekly	Chimeric anti-TNF antibody	
Golimumab	s/c, 50 mg once monthly	Fully human anti-TNF antibody	
Rituximab	iv, 1000 mg on day 0 and 14 then 6 monthly	B-cell depletion, targets CD-20	Infusion reactions
Anakinra	s/c, 100 mg daily	IL-1 receptor antagonist	Injection site reactions
Abatacept	iv, weeks 0,2,4 then 4 weekly	CTLA4-Ig, blocks co-stimulation	Headache, nausea, infection
Tocilizumab (TCZ)	iv, 8 mg/kg infused monthly	Monoclonal antibody against IL-6	Heptotoxicity, neutropenia, abnormal lipid profiles

Certolizumab, s/c, week 0/2/4: 400 mg; after 200 mg every other week; PEGylated Fab' of monoclonal antibody

o oral, *s/c* subcutaneous, *im* intramuscular, *iv* intravenous

leflunomide appears superior to other conventional DMARDs, but this combination may also be associated with increased hepatotoxicity (Gaujoux-Viala et al. 2010).

The evolution of biological therapies has provided insight into the pathogenesis of RA as well as ushering in a new era in its treatment. Currently, there are five anti-TNFs (adalimumab, etanercept, golimumab, infliximab, certolizumab), one interleukin-1 receptor antagonist (anakinra), one T-cell selective co-stimulation modulator (abatacept), one chimeric monoclonal CD20 antibody (rituximab) and one antibody against the IL-6 receptor (tocilizumab) available for the treatment of RA (Tvete et al. 2015). All biological drugs are effective when compared to placebo as well as conventional DMARDs and are generally more effective when given together with conventional DMARDs. Higher doses of biological agents are associated with higher effect compared to lower doses (Tvete et al. 2015).

Anti-TNFs have positive effects on disease activity, well-being and radiographic progression. The efficacy, onset of action and side effect profile are comparable for all anti-TNFs. Lately, certolizumab pegol, a PEGylated anti-TNF, has shown promising results in the treatment of RA. The long-term efficacy over almost 5 years in combination with MTX in patients with active RA was recently reported for certolizumab (Smolen et al. 2015).

The anti-interleukin-6 receptor antibody tocilizumab achieved significantly greater improvement in radiographic progression and physical function after 52 weeks compared to patients treated with conventional DMARDs. Tocilizumab is effective in combination with MTX and also as monotherapy for the treatment of early RA (Burmester et al. 2015). The effectiveness of tocilizumab is similar to anti-TNF with respect to treatment response as measured on the ACR20 and ACR50 (Bergman et al. 2010).

A new class of orally available small molecules, the Janus kinase (JAK) inhibitors, have recently been introduced. Tofacitinib is an inhibitor of JAK 1 and 3 and shows similar efficacy when compared to the anti-TNF agents (van Vollenhoven et al. 2012).

These new agents are costly but efficacious. Their efficacy is usually enhanced by using them in combination with MTX or leflunomide (Nam et al. 2010). Recent evidence suggests that the addition of a biologic agent to those patients who have had an inadequate response to MTX at 3 months is superior to combination conventional DMARD therapy. This may be through synergistic action or because the conventional DMARD prevents formation of neutralising antibodies against the biologic agent. Before the initiation of a biological agent, it is mandatory to screen for past exposure to *Mycobacterium tuberculosis* as the risk of reactivation of latent infection is high. This is usually with a combination of chest radiograph, Mantoux and interferon gamma release assay. Rates of infection with other organisms appear to be increased, particularly in the first 12 months. Most authorities would suggest the use of anti-TNF therapy as initial biological treatment unless contraindicated as a consequence of recent malignancy, active sepsis or hypersensitivity.

The impact of disease in RA can be assessed by looking at the three domains of disease activity, disability and structural damage. There are a number of

Table 8.4 Measures of disease activity in RA

	Formula	Moderate activity	Low activity	Remission
DAS	$0.54 \cdot \sqrt{RAI} + 0.065 \cdot SJC + 0.33 \cdot \ln(ESR) + 0.0072 \cdot \text{VAS}$	3.7	2.4	1.6
DAS28	$0.56 \cdot \sqrt{TJC} + 0.039 \cdot SJC + 0.72 \cdot \ln(ESR) + 0.0013 \cdot VAS$	5.1	3.2	2.6
SDAI	TJC + *SJC* + VAS + PhysicianVAS + CRP	26	11	3.3
CDAI	TJC + *SJC* + VAS + PhysicianVAS	22	10	2.8

well-validated tools in routine use to facilitate this process including the DAS, DAS28, CDAI, SDAI (Table 8.4) and ACR response criteria for disease activity, the Health Assessment Questionnaire (HAQ) and SF36 for disability and the Sharp-van der Heidje method for assessing joint space narrowing and erosion on plain radiograph. Full details of these measures are beyond the scope of this text. However, important targets are presented in Table 8.4.

8.3 Spondyloarthritis (SpA)

The spondylarthritides (SpA) are a group of inflammatory disorders of the spine and peripheral joints where the hallmark pathologic feature is enthesitis. The classification system for SpA has recently been revised highlighting the distinction between axial and peripheral disease which includes psoriatic arthritis (PsA), reactive arthritis, enteropathic arthritis, the enthesitis-related subtype of juvenile idiopathic arthritis and undifferentiated spondyloarthritis (Rudwaleit et al. 2011). It has been clear for many years that like RA, SpA is influenced by genetic, environmental and immunologic factors. Despite substantial progress into our understanding of these areas, it is not yet possible to link them into a unified theory of pathogenesis. In this chapter radiographic axial SpA (r-axSpA), non-radiographic axial SpA (nr-axSpA) and psoriatic arthritis (PsA) are discussed in detail.

8.3.1 Axial Spondyloarthritis

8.3.1.1 Epidemiology

The term axial SpA includes radiographic axial SpA (previously known as ankylosing spondylitis (AS) or Bechterew's disease) and non-radiographic axial spondyloarthritis according to the Assessment of Spondyloarthritis International Society (ASAS) criteria. The typical clinical feature of axial SpA is the presence of inflammatory back pain ≥3 months, age of onset below the age of 45 years, response to NSAIDs, a positive family history and HLA-B27 positivity. Associated inflammatory diseases such as inflammatory bowel disease (IBD) or uveitis are common features.

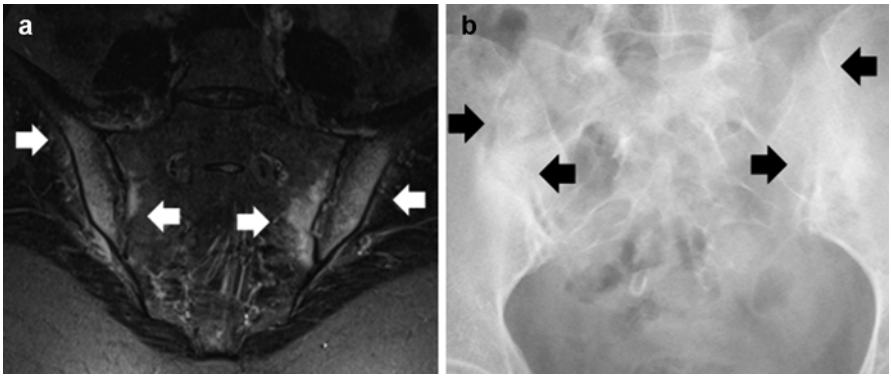

Fig. 8.2 (**a**) MRI (STIR sequence) showing signs of disease activity. *White arrows*: oedema in the bone marrow. (**b**) Pelvic X-ray film showing bilateral sacroiliitis (*black arrows*), New York Criteria 3–4

In r-axSpA, typical radiographic changes can be found with sclerosis, erosion and fusion of the sacroiliac joints as the most important findings. In contrast, nr-axSpA is distinguished by the presence of MRI changes in the absence of radiographic disease (Rudwaleit and Sieper 2012). See Fig. 8.2.

Several studies in different populations have found an annual incidence of 7 cases per 100,000 population for axial SpA. This appears to have remained constant over the last 55 years, with males affected approximately three times more frequently than females (Gabriel and Michaud 2009). Although the mean age of onset is 24–26 years, approximately 15 % experience disease onset in childhood; onset after age 45 is rare.

The incidence of axial SpA follows closely that of the HLA-B27 allele around the world and, as such, is highest in Native North Americans and lowest in Australian Aborigines and Africans (Lau et al. 1998). In white European populations, the frequency of the HLA-B27 gene ranges from 26 % in the Lapps of northern Norway to 4 % in Southern Europeans.

8.3.1.2 Pathology and Cellular Mechanisms

The pathology of SpA differs from RA in two key factors. Firstly, in SpA the enthesis is the site of major histologic changes which progress in an orderly sequence, beginning with a destructive enthesopathy followed by a healing process with new bone formation linking deeper bone to the ligament and ultimately resulting in bony ankylosis (Ball 1971). Vertebral changes typically begin with an erosive lesion at the anterior corner of the annulus fibrosus. Secondly, the healing process results in increased bone formation which is laid down initially as cancellous bone which is then remodelled into mature lamellar bone creating the typical syndesmophytes that are seen on plain radiography of the spine.

The pattern of joint involvement is different from that seen in RA with sacroiliitis, presenting as buttock pain, being a hallmark clinical feature of axial

SpA. Changes seen on plain radiology of the sacroiliac joints are most prominent towards the inferior aspects of the joints. Once disease has been longstanding, there is encasement of the joints as a result of ossification of the capsule, often surrounding small islands of intact articular cartilage. It is important to bear in mind that even in the population without axial SpA, there can be progressive fusion of the sacroiliac joint as a result of osteoarthritis; changes are more marked on the iliac side and towards the superior aspect of the joints in osteoarthritis.

Histological specimens from the hip, zygapophyseal and sacroiliac joints of patients with active disease have identified infiltrates of T-cells, B-cells, macrophages and osteoclasts as well as cells involved in angiogenesis. Synovitis is less common than in RA and can be distinguished by the greater proportion of M2 regulatory CD163+ macrophages. Expression of TNF-α and TGF-β mRNA is increased, and recent advances in treatment with therapies blocking TNF-α have shown that this cytokine is responsible for the pain, fatigue, swelling and stiffness (Francois et al. 2006). Nevertheless, neither the cell stimulating TNF-α production nor its target cell has yet been identified. Since a proportion of patients fail to achieve a complete remission with anti-TNF-α therapy, it is clear that there are still questions to be answered in this area.

Additionally, the target antigen driving the immune response has yet to be identified. However, a T-cell response against a proteoglycan link protein has been demonstrated in humans with axial SpA (Mikecz et al. 1988). In the Balb/c mouse, a clinical picture similar to axial SpA can be induced by immunisation with fetal human cartilage creating a humoral and cellular response against aggrecan (Glant et al. 1987).

8.3.1.3 Genetic and Immunologic Factors

It has long been appreciated that axial SpA are heritable diseases with genetic factors being responsible for ~90 % of the susceptibility. Evidence has come from twin studies: if a condition were entirely genetically determined, one would anticipate 100 % concordance between monozygotic twins; however, for axial SpA, only 63 % concordance is seen suggesting involvement of non-genetic factors to be discussed shortly (Jarvinen 1995).

The discovery of the association of HLA-B27 with axial SpA was made contemporaneously by two groups (Schlosstein et al. 1973; Brewerton et al. 1973). Development of the B27 transgenic rat in the 1990s confirmed the direct involvement of this molecule in the disease process (Taurog and Hammer 1995). To date, approximately 60 different subtypes of HLA-B27 have been identified that have most likely evolved from the B*2705 allele. The most common alleles, B*2702, B*2704, B*2705 and B*2707, are associated with axial disease. Interestingly, in the Sardinian population, B*2709, and, in the Southeast Asian population, B*2706 are much less common in those with axial disease (Khan 2000).

There are currently three hypotheses explaining the possible role of HLA-B27 in the pathogenesis of axial SpA. Firstly, it is known that the HLA-B27 molecule does not behave like other HLA class I molecules in that it is capable of homo-dimerising in the absence of β2-microglobulin – a process termed misfolding. It is postulated

that this stimulates NK (natural killer) and T-cells through interaction with cell surface receptors in the leukocyte immunoglobulin-like receptor (LILR) family (Kollnberger et al. 2004). Secondly, the unfolded protein response hypothesis holds that a reduced rate of folding of the HLA-B27 molecule in the endoplasmic reticulum triggers an intracellular signalling response that may in turn lead to IL-23 release. Evidence supporting this unfolded protein response has been found in synovial biopsies from patients with axial SpA, and it is known that the ERAP1 gene product is important in processing the antigenic peptide required during the folding process (Dong et al. 2008). Finally, the molecular mimicry hypothesis suggests that HLA-B27 preferentially binds to a self-antigen that resembles a microbial peptide. This is supported by the presence of T-cells that recognise self-antigens in vivo (Atagunduz et al. 2005).

The finding that the risk of developing axial SpA was 16-fold higher in first-degree relatives of those who are HLA-B27 positive compared to those who are HLA-B27 positive in the general population suggested that although HLA-B27 was important, there were likely to be additional genetic factors to be identified (van der Linden et al. 1984).

Attempts to identify other genetic factors based on a candidate gene approach have proven largely unsuccessful. However, work has progressed with the advent of whole genome scanning techniques, and, to date, there have been three published genome scans in axial SpA including one in the Han Chinese population (Laval et al. 2001; Brown et al. 2003; Gu et al. 2004; Zhang et al. 2004). Seven loci have been identified and validated by this procedure; these include HLA-B27, ERAP-1 (ARTS-1), IL-23R, IL1R2 and ANTXR2 (CMG2); the other two loci do not encode gene sequences. The population attributable risks for HLA-B27, ARTS-1 and IL23R are 90 %, 26 % and 1 %, respectively (Burton et al. 2007). The association with IL-23R has been replicated in Spanish and Canadian cohorts. Other candidate genes are TNF-α and CYP2D6. ERAP-1 is known to be involved in the processing of HLA-B27 molecules as well as in the shedding of receptors for TNF-α, IL-1 and IL-6 from the cell surface. It is therefore conceivable that defective ERAP-1 function could lead to defective cytokine regulation. IL-23R is expressed on Th17 cells, which in turn secrete IL-17, a potent pro-inflammatory cytokine that leads to the release of IL-1, TNF-α. This cell type is being subject to increasing scrutiny in spondyloarthritis as well as in RA and may offer a new therapeutic target in the future. The role of ANTXR2 is still unknown.

8.3.1.4 Environmental Factors

Since the presence of the genetic factors identified to date is neither necessary nor sufficient to initiate disease, investigators have been searching for an environmental trigger. The observation that a syndrome of arthritis, anterior uveitis and urethritis can develop after specific infections (*Campylobacter, Shigella, Salmonella, Yersinia* and *Chlamydia* species) is evidence that infection can be an initiating event for these disorders. Further work with the HLA-B27 transgenic mouse has shown that it only develops axial SpA if it is exposed to environmental pathogens in the animal house.

Indeed, intestinal colonisation with *Bacteroides* species appears to be sufficient to initiate disease in the susceptible host (Rath et al. 1996).

Antibodies against *Klebsiella* have shown an association with human axial SpA, suggesting that there may be a role for this agent in initiating or maintaining disease activity (Rashid and Ebringer 2007). The association is attractive in that it seeks to explain the association between the gastrointestinal tract and axial SpA. Whilst a small open label trial of moxifloxacin has shown promise, more work is clearly required in this area.

A final factor that has been investigated is mechanical stress at the enthesis; it is hypothesised that this leads to downstream events that ultimately result in inflammation, erosion and bone formation (Benjamin et al. 2007).

8.3.1.5 Mechanisms of Bone Erosion and Formation in Axial SpA

The analysis of histological specimens from inflamed tissues shows significant expression of the enzymes cathepsin K and matrix metalloproteinase-1 (MMP1) by the invading mononuclear cells in those with axial SpA (Neidhart et al. 2009). In contrast, those with RA demonstrate an overexpression of RANKL and MMP3 suggesting that the pathways involved in bone metabolism are different.

Evidence from animal modelling suggests involvement of the RANKL-OPG axis in axial SpA (Rauner et al. 2009). The principal mechanism of bone formation at the enthesis appears to be through endochondral ossification. Members of the bone morphogenic protein (BMP) family of growth factors influence chondrocyte development and are important early in the process. Reduced expression of the negative regulator, sclerostin, has been shown in axial SpA suggesting that this pathway may be important in vivo (Appel et al. 2009). Later stages of bone development are influenced by the Wnt signalling pathway through intracellular accumulation of β-catenin which ultimately leads to osteoblast differentiation. Reduced levels of DKK-1, which inhibit this pathway, have been found in axial SpA, and it is postulated that this may be important in syndesmophyte formation (Daoussis et al. 2010).

8.3.1.6 Diagnostic and Classification Criteria

The diagnostic criteria for axial SpA were developed in Rome in 1960 and subsequently underwent modification in New York in 1966 and again in 1984 (Goie The et al. 1985). The current ASAS criteria for the classification of SpA are shown in Fig. 8.3 (Rudwaleit 2009). The ASAS criteria should be applied to patients with chronic back pain and age of onset under 45 years old.

For the individual patient, diagnosis is often delayed because of late presentation; some patients present with features other than axial disease which can mislead the unwary, and plain radiographic changes of sacroiliitis take several years to become evident (Kidd and Cawley 1988). It is for this reason that MRI is becoming increasingly important in the early diagnosis of inflammatory spinal disease where changes are evident at a much earlier stage.

8.3.1.7 Presentation

The classical feature of axial SpA is inflammatory spinal pain. Usually felt in the lower back or buttocks, the pain is typified by its rhythm which is worst overnight

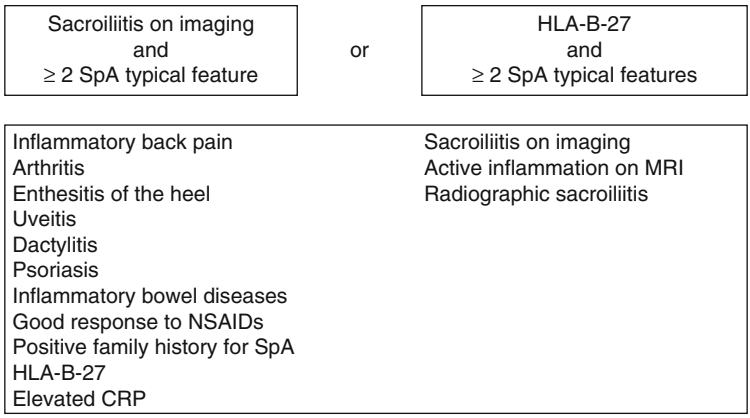

Fig. 8.3 The ASAS criteria for classification of axial spondyloarthritis for patients with chronic back pain and age onset under 45 years. Regarding sacroiliitis on imaging: either (i) unilateral sacroiliitis grade 3–4 or bilateral sacroiliitis grade 2–4 by X-rays or, (ii) active inflammatory lesions of sacroiliac joints with definite bone marrow oedema reflecting sacroiliitis by MRI (Modified by Rudwaleit et al. 2009)

or early in the morning. Many patients report prolonged stiffness making it difficult for them to dress. The stiffness and pain tend to improve over the course of the day and almost always with exercise or anti-inflammatory medications. Some patients notice that their symptoms wax and wane over time, with flare-ups followed by periods of little or no symptoms.

If peripheral arthritis is present, it is typically found in the large joints in the lower limbs, in an asymmetrical manner. Enthesitis is a frequent feature, and most often affects the Achilles tendon, plantar fascia or common extensor origin at the lateral humeral epicondyle. Dactylitis may also be seen as the swelling of an entire digit so that it takes on a sausage shape.

Extra-articular features include anterior uveitis, which can affect up to 25–40 % of patients with SpA and is typically unilateral. In adults, this presents as a painful red eye and requires urgent ophthalmological review and management to reduce the chances of complications such at cataract, posterior synechiae and vision loss. The majority of cases in children are asymptomatic, and regular screening is warranted in this population.

Colonoscopic evaluation has found subclinical lesions in 20–70 % of cases, and it was this association that led to the routine use of sulphasalazine for the treatment of axial spondyloarthritis. The corollary of this is that approximately 30 % of patients with inflammatory bowel disease have axial disease; 10–20 % having sacroiliitis alone, 7–12 % having spondylitis and 10 % having features indistinguishable from classical axial SpA.

Other features seldom seen in practice are secondary amyloidosis due to deposition of serum amyloid A protein, apical lung fibrosis, aortitis and cardiac conduction defects due to fibrosis of the conduction system. Rarely, in longstanding axial

disease, cauda equina syndrome can develop, and arachnoid diverticulae are described.

It should be evident from the preceding discussion of clinical features that a careful examination can reward the examiner with plentiful signs. Of particular importance is assessment of spinal motion, and this is carried out to best advantage with a physiotherapist so that intervention can be directed appropriately. The modified Schober's test is performed to assess the range of lumbar flexion; lateral lumbar bending is assessed by finger-floor distance and the extent of cervical lordosis by a tragus-wall distance. This latter measure being preferred over the occiput-wall distance as the tragus lies closer to the centre of rotation of the skull on the atlas and is relatively unaffected by the degree of neck flexion and extension. Chest expansion and hip range of motion should also be included in routine measurement.

Imaging has always been an important factor in making the diagnosis, reflecting the presence of sacroiliitis in the diagnostic and classification criteria. As mentioned above, the characteristic findings are within the axial skeleton where early changes include sacroiliitis which can be detected on MRI or CT in the early stages or visualised on plain radiograph once disease has been present for several years. Family studies have suggested that a mean of 9 years is required for plain radiographic changes to become apparent after changes are first detected on MRI. "Bright corners" or Romanus lesions may be seen on plain radiography or MRI in the antero-superior or antero-inferior corners of the vertebral bodies reflecting marginal erosion with reactive sclerotic change. Eventually, this leads to squaring of the vertebral body and finally to ossification of the superficial layers of the annulus fibrosus and longitudinal ligaments forming the typical, end-stage bamboo spine of axial SpA. Some may develop single or multilevel spondylodiscitis (Andersson lesions), which can be mistaken for septic discitis or osteomyelitis.

With the implementation of MRI in routine clinical practice, sacroiliitis can be observed even in the early stages of disease. This has led to the concept of nr-axSpA. Other than the higher proportion of female subjects in nr-axSpA studies, no major differences in patient demographics have been observed between r-axSpA and nr-axSpA. The rate of progression from nr-axSpA to r-axSpA was reported to be about 12 % after 2 years of follow-up (Calin et al. 1994). Given the similarity in the level of symptoms and the response to treatment, nr-axSpA seems to be an early stage of radiographic disease (Corli et al. 2015).

Factors predicting poor prognosis include hip involvement, ESR > 30 mm/h, lack of response to NSAIDs, reduced spinal motion, dactylitis, oligoarticular arthritis, age of onset less than 16 and the presence of inflammatory bowel disease, psoriasis or urethritis (Amor et al. 1994).

8.3.1.8 Assessment and Monitoring of Disease Activity

It is an unfortunate fact that about 40 % of patients with clinically and radiologically active axial disease do not reflect this with a rise in their serum inflammatory markers. Nevertheless, the ESR and CRP are commonly monitored as they have prognostic implications, and in some countries, a sufficient rise in these markers is required for funding of anti-TNF therapy.

Numerous tools have been developed to facilitate both the assessment of activity at one point in time and the change in disease activity over time. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a validated six-item questionnaire that asks patients to mark the severity of their pain, stiffness and fatigue on visual analogue scales. A score of 4 or greater is consistent with active diseases, and a change of 50 % is considered significant for assessing the efficacy of interventions. Functional limitation can be quantified with numerous composite measures such as the BASFI (Bath Ankylosing Spondylitis Functional Index), HAQ or WOMAC scores. In practice, the BASFI is used most commonly and consists of a ten-item questionnaire on activities of daily living.

Primarily for use in clinical trials, there are response criteria to assess the efficacy of interventions in AS. The Ankylosing Spondylitis Assessment Score (ASAS 20) response criteria are fulfilled if there is a 20 % reduction on patient global assessment, function (as measured on the BASFI), pain and inflammation (Anderson et al. 2001).

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in axial SpA. ASDAS includes back pain, duration of morning stiffness, patient global assessment, peripheral pain/swelling as well as CRP or ESR and is able to discriminate between high and low disease activity in early SpA (Fernández-Espartero et al. 2014).

8.3.1.9 Treatment of Axial SpA

Comparable to the treat-to-target (T2T) concept in RA, the primary treatment goal in axial SpA is defined as remission, with a secondary objective defined as low disease activity (Smolen et al. 2014). The ASAS/EULAR recommend maximising long-term health-related quality by controlling symptoms and inflammation. Moreover, an additional objective of therapy is the prevention of progressive structural damage. The optimal therapy in axial SpA therefore requires a combination of pharmacological and non-pharmacological treatments.

The wide array of potential symptoms and sites of disease involvement means that the treatment has to be tailored to the individual with the overall aims being to reduce pain, maintain mobility and function and possibly modify the underlying disease process.

Patient education is a principal component of any effective management strategy. Group education programmes are offered in some centres, and although comparison of these is not possible because of the heterogeneous nature of the different groups, many believe that they promote coping with the emotional consequences of the disease and help patients participate in the management. The role of education is acknowledged in the EULAR practice recommendations as a cornerstone to effective management (Zochling et al. 2006).

The importance of early and regular physical therapy in axial SpA is of the utmost importance; for many years, it was the sole management for the condition. There is evidence from a well-conducted but small multicentre trial that physical therapy in addition to medical management resulted in better spinal mobility, chest expansion and work capacity than medical management alone (Ince et al. 2006).

The best form of physical therapy is still debated; however, multimodal programmes encouraging stretching and aerobic exercise seem appropriate for most, and others with specific issues may merit tailored programmes.

For axial disease, NSAIDs and physical therapy should be considered first-line interventions. Approximately 70–80 % of patients with axial SpA will derive benefit from NSAIDs compared to only 15 % of those with non-inflammatory lower back pain. Analysis of the data from randomised trials of NSAID used in axial SpA has suggested that all patients received maximum benefit within 2 weeks, and this would therefore seem an appropriate length of treatment trial. Approximately 10–60 % will develop minor gastrointestinal side effects including epigastric pain and nausea, but serious side effects such a gastrointestinal bleeding occur in 2–4 % treated for 12 months. The risk of serious adverse events rises with age, comorbidity and concomitant use of other anti-inflammatory agents. Agents selective for the COX-2 isoenzyme have less gastrointestinal toxicity; however, this has to be balanced with the well-documented rise in cardiovascular events with these agents. It has even been suggested that regular use of NSAIDs – taken daily rather than as needed – can retard radiographic progression. The above measures will control symptoms adequately in approximately 70 % of patients; however, in those with ongoing symptoms, high inflammatory markers, high score on the BASDAI or evidence from imaging that disease is progressing, further treatment is required.

There is now widespread recognition that conventional DMARDs such as leflunomide or methotrexate are not effective for the control of axial disease. Similarly, there is a very limited role for systemic corticosteroids in axial SpA, but intra-articular steroids, given either into a peripheral joint or in to the sacroiliac joint, can provide substantial symptomatic benefit. As a consequence, TNF inhibitors should be considered in the event of high disease activity with or without prior conventional DMARD therapy in patients with axial disease (Braun et al. 2011).

Randomised controlled trials have been conducted showing that improvement can be seen as early as 2 weeks and is maximal after 12 weeks. This can be sustained over several years (van den Bosch et al. 2001; Braun et al. 2002; Gorman et al. 2002; Brandt et al. 2003; Davis et al. 2003; Calin et al. 2004; van der Heijde et al. 2005, 2006; Lambert et al. 2007). In addition, these agents are associated with improvement in quality of life, reduced sick leave, improved work productivity and reduction in inflammation on MRI. Even patients with complete spinal ankylosis report symptomatic benefit from these agents.

Early remission under anti-TNF therapy was reported to be the strongest predictor for achieving remission for up to 5 years in axial SpA. In the ATLAS trial, patients receiving adalimumab and achieving remission after 12 weeks were more than ten times more likely to be in remission after 5 years compared to patients who did not reach remission after 12 weeks (Sieper et al. 2012). In the ABILITY-1 trial, effective disease control has also been reported in nr-axSpA patients treated with adalimumab. Decreased inflammation and improved quality of life were also shown in this study. Patients with age < 40, symptom duration < 5 years or high baseline C-reactive protein demonstrated a better response at week 12 of treatment (Sieper et al. 2013).

Similar results after 1 year of etanercept treatment were shown in r-ax-SpA and nr-ax-SpA. The ankylosing spondylitis disease activity scores and BASDAI were decreased in r-ax-SpA and nr-ax-SpA, and the response rate to etanercept was similar in the two groups (Song et al. 2013).

In patients with nr-axSpA who had an insufficient response to NSAIDs, etanercept treatment showed significant benefits with regard to function, disease activity and inflammation as shown on MRI at week 12 when compared to placebo (Dougados et al. 2013). Recently, the efficacy and safety of certolizumab pegol, a PEGylated Fc-free anti-TNF, were shown in the RAPID-axSpA trial patients with r-ax-SpA and nr-axSpA. Response rates measured by ASAS-20 were significantly higher in certolizumab when compared with placebo. The treatment response was similar for certolizumab in r-ax-SpA and nr-axSpA, and both subgroups improved in BASDAI (Landewé et al. 2014).

Despite the quick response to anti-TNFs, the improvement in disease-related quality of life, augmented physical mobility and reduced pain, the response rate after discontinuation is high in r-ax-SpA and nr-ax-SpA. A relapse rate of approximately 70 % was reported in patients with r-ax-SpA and nr-ax-SpA (Haibel et al. 2013). These data suggest that discontinuation of biologics is associated with an increased risk of relapse in axial SpA, and discontinuation should be carefully considered.

A positive effect regarding inhibition of radiographic progression in patients with axial SpA treated with anti-TNFs has not been shown in most trials, suggesting that osteoproliferation in axial SpA is independent of anti-TNF treatment (van der Heijde et al. 2009). However, in patients treated with infliximab, bony spinal lesions progressed more slowly (Baraliakos et al. 2005).

Biologic agents appear to be of similar efficacy for treating axial disease with best responses seen in younger patients with high inflammatory markers and active disease on MRI. Anecdotally however, adalimumab and etanercept are given in fixed dosage regimens and for larger patients, and those with very active disease, response may be improved with infliximab as the dose can be adjusted to body weight. In addition, anterior uveitis can develop in those receiving etanercept, and so this agent may not be preferred in patients where this is a prominent feature.

For peripheral disease, the anti-TNF agents show excellent efficacy. Prior to their introduction, studies had focussed on the use of sulphasalazine as a consequence of the link with inflammatory bowel disease. To date, ten randomised, double-blind studies including two multicentre studies have been conducted assessing the efficacy of this agent in peripheral arthritis and finding it to be of modest efficacy (Dougados et al. 1995; Clegg et al. 1996). A subsequent meta-analysis of four trials concluded that the duration and severity of morning stiffness, pain severity and patient global assessment of disease activity reached statistical significance.

Approximately 30 % of patients with axial SpA will not respond to treatment with anti-TNF therapy or will experience side effects leading to its discontinuation. Trials are underway using anti-IL-6, anti-IL-23, anti-17A and targeted B-cell therapy. The IL-6-inhibition by tocilizumab did not demonstrate efficacy in patients with axial SpA (Sieper et al. 2014). However, in a pilot study on the IL-17A-inhibitor

secukinumab, treatment up to 2 years was associated to clinical improvement accompanied by regression of spinal inflammation (Baraliakos et al. 2015). There is evidence from one small study that the intravenous bisphosphonate, pamidronate, given in a dose of 60 mg once monthly improved symptoms (Maksymowych et al. 2002). Although it is not helpful in the presence of peripheral joint synovitis, it also has the advantage of treating the well-documented association of AS with osteoporosis.

8.4 Psoriatic Arthritis (PsA)

8.4.1 Epidemiology

Psoriatic arthritis (PsA) is a chronic inflammatory joint disorder with a prevalence of 30 % in patients with skin psoriasis. PsA is characterised by local bone loss and new bone formation. Bone erosions are as frequent as in RA, although have a different morphology (Finzel et al. 2011). PsA is associated with nail disease (which has recently been shown to be a form of enthesitis), uveitis and inflammatory bowel disease (Aydin et al. 2012; Veale 2013). In 75 % of cases, skin involvement precedes the onset of joint disease, which can be delayed by up to 10 years (Duarte 2012). Although the pathophysiology is not fully understood to date, genetic and environmental factors have been discussed (see Sect. 8.3.1).

8.4.2 Diagnostic and Classification Criteria

Based on the ASAS criteria, peripheral arthritis, enthesitis or dactylitis and SpA-typical parameters such as uveitis, HLA-B27-positivity and skin psoriasis lead to the diagnosis of PsA with a sensitivity of 77.8 % and a specificity 82.9 % (Rudwaleit et al. 2011). The CASPAR classification criteria (*ClASsification* criteria for the diagnosis of *P*soriatic *AR*thritis) include inflammatory joint, spine or entheseal disease plus at least three points: (i) symptomatic psoriasis (two points), family history for psoriasis (one point) and psoriasis in the past (one point); (ii) psoriatic nail disease (one point); (iii) rheumatoid factor negativity (one point); (iv) symptomatic dactylitis (one point) and dactylitis in the past (one point); and (v) periarticular bone formation (one point) (Taylor et al. 2006).

8.4.3 Treatment of PsA

EULAR recommends NSAIDs as first-line therapy for the management of PsA. To prevent joint damage, synthetic DMARDs in combination with local injections of glucocorticoids should be considered in patients with active disease, even at an early stage of the disease (Gossec et al. 2012). Systemic glucocorticoids are not recommended for the chronic use due to the potential risk of a withdrawal flare of psoriasis.

In contrast to RA, MTX and other conventional DMARDs are less effective in PsA, as has been shown previously. Low-dose oral MTX does not seem to improve synovitis in active PsA (Kingsley et al. 2012). Only parenteral high-dose MTX and salazopyrin had well-demonstrated effects in a Cochrane analysis of PsA patients (Jones et al. 2000).

TNF-α inhibitors should be considered in patients with active arthritis and an inadequate response to at least one conventional DMARD and in patients with active enthesitis or dactylitis and an insufficient response to local steroid injection and NSAIDs. For very active PsA characterised by structural joint damage, numerous swollen joints and extensive skin disease, biologics should also be considered in the treatment of naive patients. Moreover, biological drugs are especially beneficial in those with mainly axial disease and insufficient response to NSAIDs.

Positive effects for anti-TNFs on disease activity, enthesitis, dactylitis, skin psoriasis and psoriatic nail disease have been reported (Ritchlin et al. 2009; Mease et al. 2000; Kavanaugh et al. 2009). A reduced rate of radiographic progression was shown in PsA patients treated with anti-TNFs compared to conventional DMARDs (Glintborg et al. 2011; Eder et al. 2014). Currently six biological agents are available for the treatment of PsA (etanercept, adalimumab, infliximab, golimumab, certolizumab and ustekinumab). A similar efficacy regarding peripheral arthritis, ACR-50 response after 24 weeks of therapy, the reduction of radiographic progression and the improvement of skin disease was shown for the anti-TNFs (Fénix-Caballero et al. 2013; Ritchlin et al. 2009).

The IL-12/IL-23-antibody ustekinumab was recently approved for the treatment of PsA as well as plaque psoriasis. Ustekinumab treatment reduced joint disease activity and improved quality of life in patients with PsA (Gottlieb and Narang 2013). In the phase 3 trials PSUMMIT I and PSUMMIT II, a significant reduction in radiographic progression of joint damage in patients with active PsA and ustekinumab therapy compared to placebo was shown (Kavanaugh et al. 2014a; 2015).

Another emerging therapeutic area is the inhibition of IL-17A. Secukinumab, a fully human monoclonal antibody, is a promising biological agent in the treatment of PsA and skin psoriasis (McInnes et al. 2014). PsA patients treated with secukinumab showed a significantly higher response rate after 24 weeks and less structural damage compared to those receiving placebo in a phase 2 trial. The infection rate was higher in the secukinumab group than in the placebo group (Mease et al. 2015).

The oral phosphodiesterase-4-inhibitor apremilast showed significant benefits regarding disease activity, skin psoriasis and physical function in phase III studies, with an acceptable safety profile (Kavanaugh et al. 2015b). Apremilast has recently been approved in the USA and Europe.

8.4.4 Systemic Bone Loss in RA and SpA

It has been appreciated for some time that the quality of bone in RA is adversely influenced by the inflammatory response. This is evident as periarticular osteopenia and well as generalised osteoporosis. Therefore, RA is an independent risk factor for secondary osteoporosis. Both vertebral and non-vertebral fracture risk is increased in patients with

RA (Vis et al. 2011; Kim et al. 2010; Dirven et al. 2012; Wright et al. 2011). The increased risk of fracture is most marked in the spine (RR 2.4) and at the hip (RR 1.8). Furthermore, the fracture risk is increased substantially by the use of glucocorticoids (van Staa et al. 2006). Recently, microstructural deteriorations were reported in RA. A decreased trabecular bone volume caused by a decrease in trabecular width and a low trabecular number in female and male RA patients was reported. In addition, cortical thinning with an increase in the cortical perimeter, reflecting a compensatory mechanism to restore bone strength, was found (Kocijan et al. 2014a). Changes of the volumetric BMD, bone volume and inhomogeneity of the trabecular network as well as higher cortical porosity were found in Asian patients with RA (Zhu et al. 2013, 2014).

Besides inflammation, autoimmunity seems to play a major role not only in local but also in systemic bone loss in RA. Patients with seropositive RA (ACPA or rheumatoid factor positive) suffered from more severe systemic bone loss, characterised by deterioration of both trabecular and cortical bone (Kocijan et al. 2014b). The diagnosis of RA was suggested as an independent risk factor for osteoporosis and low-traumatic fracture risk and therefore included in the fracture risk assessment tool (FRAX) (McCloskey et al. 2012).

The relationship between SpA and spinal osteoporosis has been well documented. Spinal fracture may account for some of the exaggerated kyphosis seen in many patients with longstanding disease (Ghozlani et al. 2009). Fracture of the rigid spine can occur with minimal trauma and is usually longitudinal across a syndesmophyte rather than across a vertebral body. As in RA, bone quality is reduced in SpA. The incidence of spinal osteoporotic fractures is increased (Magrey and Khan 2010). Data regarding systemic bone loss in PsA are conflicting. Low, normal and high area bone mineral (BMD) were reported in PsA (Frediani et al. 2001; Attia et al. 2011; Millard et al. 2001; Nolla et al. 1999; Borman et al. 2008; Riesco et al. 2013). Using high-resolution peripheral quantitative computed tomography (HR-pQCT), significant alterations in trabecular, but not cortical bone structure, were observed (see Fig. 8.4, Kocijan et al. 2015). The duration of skin psoriasis was an independent risk factor for patients with PsA. Moreover, significant associations between mean psoriatic disease duration and BMD alterations (D'Epiro et al. 2014) as well as the presence of non-vertebral fractures (Del Puente et al. 2015) were reported.

Fig. 8.4 Bone microstructure in psoriatic arthritis (*PsA*) and healthy control (*CTRL*). Reconstruction of high-resolution peripheral quantitative computed tomography scans; 3D reconstruction, 60 slices, axial/sagittal view

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