

19.5 Rheumatoid arthritis

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ESSENTIALS Rheumatoid arthritis is a common, painful, and disabling auto- immune disease affecting 0.5 to 1.0% of adults, with a female:male ratio of 2.5:1. Clinical features Rheumatoid arthritis is characterized by both synovial and systemic inflammation. Synovitis classically presents as a symmetrical destruc- tive polyarthritis affecting the hands and feet typified by episodic pain, stiffness, and swelling. Systemic inflammation commonly leads to fa- tigue, weight loss, and depression. Other extra-articular manifestations include accelerated atherosclerosis, interstitial lung disease, nerve and spinal cord compression, scleritis, vasculitis, rheumatoid nodules, and haematological abnormalities such as anaemia and Felty's syndrome. If left untreated, patients can rapidly develop irreversible joint damage leading to chronic pain, deformity, disability, and premature mortality. Aetiology, pathogenesis, and diagnosis Rheumatoid arthritis is best conceptualized as a syndrome of dysregulated chronic inflammation in which the causal pathogenic pathways vary between patients but ultimately lead to a common disease phenotype. The aetiology is multifactorial and involves an interplay between genetic factors and environmental insults such as tobacco smoking, with immune dysregulation developing over sev- eral years prior to the onset of clinical disease. The defining macroscopic feature of chronic synovitis is rheuma- toid pannus, a potent inflammatory infiltrate which causes cartilage destruction and bone erosion. Most immune cells have been impli- cated in pathogenesis, with CD4+ T cells and B lymphocytes having central roles. Furthermore, joint stromal cells are likely to actively contribute towards and perpetuate the disease. Rheumatoid arthritis is a clinical diagnosis based largely upon history and examination, supported by a limited range of investiga- tion findings including elevated levels of acute-phase reactants (e.g. C-reactive protein), the presence of autoantibodies (e.g. rheuma- toid factor and anti-citrullinated peptide antibody), and the visu- alization of synovitis on imaging (e.g. musculoskeletal ultrasound). International consensus classification criteria have been developed to aid in the standardization of research, but these are only valid after exclusion of the broad range of

differential diagnoses. Prognosis and management The past two decades have witnessed a revolution in rheumatoid arthritis outcomes, from a disease in which progressive deformity and disability were inevitable to one where remission is a realistic and achievable aim for many patients. This has been achieved by the rapid initiation of disease-modifying anti-rheumatic drug (DMARD) therapy at initial clinical presentation, with a treat-to-target approach delivered holistically via a multidisciplinary team in which the rheumatologist plays a central coordinating role. Conventional synthetic DMARDs (csDMARDs) are the anchor of rheumatoid arthritis therapy, with methotrexate the recommended first-choice DMARD. Alternative agents include sulfasalazine, hydroxychloroquine, and leflunomide. Multiple csDMARDs are often used together in combination therapy when required to achieve adequate disease control. Many of these drugs carry the risk of potentially serious adverse effects such as bone marrow suppression and hepatitis, hence regular blood monitoring is generally required. Biological drugs (monoclonal antibodies and soluble receptors) are usually reserved for those who fail to achieve adequate disease control with csDMARD therapy, which is usually continued alongside biologic therapy to both maximize therapeutic response and retard the development of anti-drug antibodies. A wide range of biologic approaches are available, including: (a) TNF inhibition (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol); (b) B-cell depletion (rituximab); (c) IL-6 receptor blockade (tocilizumab, sarilumab); and (d) co-stimulation blockade (abatacept). All of these agents carry a risk of serious infection, for example mycobacterial infections, with TNF inhibition. There are no biomarkers that reliably predict response to biologic therapy, and the sequence of biologic use is largely dictated by clinician experience. The high cost of biologic therapy is falling with the introduction of biosimilar agents. Targeted synthetic DMARDs (tsDMARDs—tofacitinib and baricitinib) inhibit the Janus kinases (JAKs), and block signalling through various cytokine and haematopoietic growth factor receptors, dependent on their precise selectivity. They are also used after the failure of csDMARD therapy, though not in combination with biologics. They have been introduced relatively recently but their adverse effects appear similar to biologics except for an enhanced risk of herpes zoster reactivation. Glucocorticoids are helpful as bridging therapy to provide temporary control of arthritis flares until DMARD therapy has taken effect.

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section 19 Rheumatological disorders 4416 effect. They can be administered locally by intra-articular or tendon sheath injection, or systemically by oral or intramuscular routes. However, their considerable side effect profile restricts their use as maintenance therapy in all but those patients who fail to respond to maximal DMARD and biologic therapy, or those in whom these are contraindicated. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in relieving arthritis pain, but long-term use is limited by their potential cardiovascular, renal, and gastrointestinal toxicities. With optimal care patients can achieve and retain disease remission with maintenance of employment and quality of life. Nevertheless, rheumatoid arthritis is a life-long autoimmune disease, requiring long-term treatment. The ultimate goal of restoration of immune self-tolerance remains elusive. Introduction Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial and systemic inflammation. The hallmark of rheumatoid arthritis is inflammation of the synovium (synovitis), which classically presents as a symmetrical polyarthritis principally affecting the small joints of the hands and feet. If left untreated, irreversible joint destruction can rapidly ensue with consequent permanent deformity and disability. For this reason, arthritis is the most visible and hence well-recognized consequence of the disease. Nevertheless, rheumatoid arthritis is a systemic disorder with significant inflammation occurring outside of the joints. These extra-

articular features include accelerated atherosclerosis, pulmonary disease, and neurological sequelae, all of which contribute to excess morbidity and mortality. Thus, as with all multisystem rheumatologic disorders, it is vital that the physician adopts a holistic approach to the patient with rheumatoid arthritis. Historically, most patients diagnosed with rheumatoid arthritis suffered relentless joint destruction, progressive disability, and poor quality of life. The past two decades, however, have witnessed a revolution in rheumatoid arthritis management, with vastly improved outcomes. The treatment paradigm has shifted to one of early intervention and the aggressive targeting of inflammation using drug combinations as well as biological and synthetic drugs targeted to key pathways in rheumatoid arthritis pathogenesis. With these advances have come remarkable improvements in morbidity and mortality, with disease remission now a realistic and achievable target for many patients.

Aetiology The precise mechanisms by which self-tolerance is breached in rheumatoid arthritis remain elusive. Most experts now agree that rheumatoid arthritis is not a single disease entity but rather a syndrome of dysregulated chronic inflammation in which the causal pathogenic pathways vary between patients. Increasing evidence supports critical roles for both genetic and environmental aetiological factors. A disease model has emerged whereby environmental insults act upon a genetically predisposed individual to cause breach of tolerance, immune dysregulation and, ultimately, clinical rheumatoid arthritis. It is important to recognize that autoreactivity, the propensity to generate immune responses against self, is common in the healthy population, but in autoimmunity this process has become dysregulated and pathological.

Genetic factors Evidence to support the importance of genetic factors in rheumatoid arthritis susceptibility first emerged from twin studies. Probandwise concordance (i.e. the probability of a twin developing rheumatoid arthritis conditional upon their cotwin having already developed the disease) is 22–35% for monozygotic twins and approximately 7% for dizygotic twins. Nevertheless, monozygotic twin concordance in rheumatoid arthritis is much lower compared with other common autoimmune disorders (Table 19.5.1), emphasizing the significant aetiological contribution of environmental factors.

HLA-DRB1 and the ‘shared epitope’ hypothesis The major histocompatibility complex (MHC) is a cluster of genes located on the short arm of chromosome 6 which play important roles in the immune response. Most of the MHC comprises the highly polymorphic human leukocyte antigen (HLA) genes which encode for MHC class I (HLA-A, HLA-B and HLA-C) and class II (HLA-DP, HLA-DQ and HLA-DR), that are critical antigen-presenting molecules. There are hundreds of different HLA alleles and therefore a multitude of combinations. However, certain groups of alleles tend to be inherited together in blocks known as haplotypes, with marked variation between geographically and ethnically distinct populations. Of particular importance to the aetiology of rheumatoid arthritis are the MHC-II molecules, which comprise an invariant α and polymorphic β chain. MHC-II is constitutively expressed at the surface of professional antigen-presenting cells (APCs) such as dendritic cells, B cells, and macrophages. In the extracellular region of the molecule a highly variable region of the β -chain forms part of a groove which binds short antigenic peptides. The MHC-II-peptide complex is then recognized by CD4⁺ helper T cells as the first critical stage of the adaptive immune response. Early studies identified a link between specific HLA-DR alleles (for example, HLA-DRB1*0101, *0401, and *0404) and the presence of rheumatoid arthritis. These alleles share specific amino acids within the peptide binding groove, known as the ‘shared epitope’. The most favoured explanation for this association is that autoantigens important in the initiation of rheumatoid arthritis bind to shared epitope-containing HLA-DR molecules with high affinity. Although the precise autoantigens in rheumatoid arthritis remain elusive, there is now good evidence for a role for citrullinated peptides (see next section).

Table 19.5.1 Probandwise concordance rates for common autoimmune diseases in monozygotic (MZ) and dizygotic (DZ) twin

studies. Higher concordance in MZ compared to DZ twins suggests a relatively greater contribution of genetic factors to the aetiology of the disease

Disease	Percentage MZ probandwise concordance	Percentage DZ probandwise concordance
Rheumatoid arthritis	22–35.3	0–6.9
Ankylosing spondylitis	40.4	3.3
Systemic lupus erythematosus	20–39.3	0–3.2
Type I diabetes mellitus	23–64.3	3–20.8
Coeliac disease	83.3–91.6	7–20
Psoriasis	72	17
Crohn's disease	58.3–62.5	0–3.8

Adapted from Journal of Autoimmunity, volume 38, Bogdanos et al, Twin studies in autoimmune disease: Genetics, gender and environment, pages J156–J169. Copyright 2012, with permission from Elsevier.

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The advent of high-throughput genomic sequencing has fuelled a surge of genome-wide association studies (GWAS). In these studies, entire genomes of many thousands of patients with a particular disease are compared with healthy controls at hundreds of thousands of common sequence variants known as single nucleotide polymorphisms (SNPs). SNPs that are more commonly inherited by rheumatoid arthritis patients are assumed to be in, or close to, predisposing genes. Multiple GWAS have identified an increasing number of SNPs associated with rheumatoid arthritis (Fig. 19.5.1). Several of these fall within genes involved in pathways that are already incriminated in rheumatoid arthritis pathogenesis, whereas others highlight novel potential pathways. Many disease-associated SNPs lie within intergenic regions, probably highlighting regulatory genetic elements with effects on both nearby and distant genes. Protein tyrosine phosphatase nonreceptor type 22 (PTPN22, also known as Lyp), is an intracellular protein important in the regulation of lymphocyte responses. A SNP in the PTPN22 gene (1858C to T) results in a single amino acid change at position 620 (arginine to tryptophan). This R620W mutation has been associated with a range of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus (SLE) and myasthenia gravis. It has the strongest non-MHC genetic association with rheumatoid arthritis and, while its precise pathogenic contribution has not been defined, highlights the fact that many rheumatoid arthritis-associated genes are immuno-regulatory.

Epigenetic factors

Epigenetics refers to heritable differences in gene expression that do not reflect the primary DNA base-pair sequence. Epigenetic mechanisms include DNA methylation, histone methylation and acetylation, noncoding RNAs such as microRNAs, and small ubiquitin-related modifier (SUMO) proteins, all of which can modify gene expression. Epigenetic changes can be triggered by environmental influences and several studies have identified epigenetic 'signatures' in rheumatoid arthritis. For example, increased expression of specific microRNAs, such as miR155, has been observed in rheumatoid arthritis synovial tissue. Although the net effect of epigenetic modification is complex and currently poorly understood, the epigenetic regulation of predisposing genes is likely to play an important role in the aetiology of rheumatoid arthritis.

Environmental factors

Smoking

Smoking is a potent epigenetic modifier and strong evidence links cigarette smoking to both an increased risk of developing rheumatoid arthritis and increased disease severity. Furthermore, epidemiological studies demonstrate a multiplicative interaction between smoking, shared epitope, and the PTPN22 R620W mutation. Consequently, an individual with all three risk factors is more than 20 times more likely to develop anti-citrullinated peptide autoantibody (ACPA) positive rheumatoid arthritis compared to an individual with none (Fig. 19.5.2). Exposure to cigarette smoke is known to induce peptidyl-arginase deiminase (PADI) enzymes, which post-translationally modify arginine to citrulline residues in a process known as citrullination or deimination. Combined with the observation that citrullinated peptides bind more readily to shared epitope-containing HLA-DR molecules, this helps to build a model linking smoking, genetic predisposition, and the development of rheumatoid

arthritis. Fig. 19.5.1 Relative contributions of single nucleotide polymorphisms (SNPs) to the risk (odds ratio) of developing rheumatoid arthritis. Aside from a few strongly associated mutations, most SNPs confer only a small increased risk. Reprinted from Journal of Autoimmunity, volume 64, Messemaker et al, Immunogenetics of rheumatoid arthritis: understanding functional implications, pages 74-81. Copyright (2015), with permission from Elsevier. Any R620W, smoking No R620W, smoking REF Any R620W, no smoking No R620W, no smoking Double SE Single SE No SE 25 Anti-CCP-positive RA 20 10 5 0 15 Odds ratio of developing ACPA+ RA Fig. 19.5.2 Interaction between smoking, shared epitope (SE) and PTPN22 R620W allele upon the risk of developing anti-citrullinated peptide antibody (ACPA)-positive rheumatoid arthritis. REF, reference. Reprinted from The American Journal of Human Genetics, volume 80, Källberg et al, Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis, pages 867-875, copyright 2007 by the American Society of Human Genetics, with permission from Elsevier.

section 19 Rheumatological disorders 4418 Infection Many pathogens contain proteins that are similar or identical to human proteins. An immune response against the pathogen could thus theoretically trigger autoimmunity in a process termed molecular mimicry. Indeed, infection is a recognized trigger of autoreactivity in conditions such as rheumatic heart disease, post-streptococcal glomerulonephritis, and reactive arthritis. These observations have led to inevitable speculation that infections may play a causative role in rheumatoid arthritis. Indeed certain chronic infective conditions are associated with rheumatoid arthritis, such as chronic periodontitis and bronchiectasis, although not necessarily via molecular mimicry. For example, *Porphyromonas gingivalis*, which is present in dental caries, expresses PADI enzymes which could citrullinate host proteins and trigger autoreactivity and, in a genetically predisposed host, autoimmunity.

Microbiome There has been a surge of recent interest in the role of the human commensal microflora, or 'microbiome', in the aetiology of autoimmune disease. It is estimated that the human gut alone contains 10 times more microbes than the number of cells in the body, with additional complexity in the oral and pulmonary mucosae. With an average of 65% genetic variation between the microbiome of different individuals, and the delicate symbiotic relationship that exists at mucosal surfaces, the microbiome is an attractive and potentially powerful environmental trigger for autoimmune disease. Evidence from mice reared in germ-free environments provides proof of principle for the role of the microbiome both in the initiation and regulation of autoimmunity. Although the exact mechanisms remain unclear, it appears that both beneficial and potentially pathogenic immune responses can be triggered by intestinal bacteria. Therapeutic manipulation of the microbiome is possible by dietary modification, antibiotics or even the adoptive transfer of faecal matter from healthy individuals in a process termed 'faecal transplantation'. The effectiveness of these approaches in the prevention or treatment of rheumatoid arthritis remains to be established but could prove to be particularly attractive in predisposed but healthy individuals.

Hormonal The excess female prevalence of rheumatoid arthritis, and a heightened incidence post-partum and peri-menopausally, suggest a likely role for sex hormones in disease aetiology. Breast feeding and age at menarche may also have an influence but studies are conflicting. Several studies have suggested that the oral contraceptive pill may be protective against rheumatoid arthritis but data on hormone replacement therapy are inconclusive. Many patients attribute the onset of rheumatoid arthritis and flares in disease activity to periods of emotional or physical stress. Although there is evidence for dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis in established rheumatoid arthritis, there is limited evidence for an aetiological role. Diet

Patients often report that diet influences the activity of their arthritis, although there is a lack of robust supportive evidence from randomized controlled trials. Nevertheless vegetarian, and particularly Mediterranean, diets appear to protect against rheumatoid arthritis as well as reducing rheumatoid arthritis pain, possibly due to the high levels of anti-oxidants they contain. Dietary supplements such as fish oils rich in omega-3 polyunsaturated fatty acids may also have anti-inflammatory effects in rheumatoid arthritis. A recent meta-analysis demonstrated a negative relationship between alcohol intake and ACPA+ RA suggesting a possible protective role of alcohol consumption in moderation. In contrast, red meat may increase the risk of inflammatory arthritis. Recent interest has focused on the role of vitamin D, with the suggestion that low levels could explain the higher prevalence of rheumatoid arthritis in Northern latitudes. Observational studies suggest that vitamin D may also reduce disease activity in rheumatoid arthritis and have cardio-protective effects, although contradictory studies also exist. Environmental toxins Occupational exposure to silica dust has been associated with an increased risk of rheumatoid arthritis in case-control and cross-sectional studies, particularly in male smokers. Organic solvents and mineral oils have also been incriminated. Furthermore, rheumatoid arthritis incidence is higher in urbanized areas, suggesting a potential role for other airborne pollutants. 'Pre-RA' and a model of rheumatoid arthritis aetiology Intriguing insights into rheumatoid arthritis aetiology have arisen from the retrospective analysis of stored serum samples from individuals who subsequently developed rheumatoid arthritis. The results of these studies are remarkable in demonstrating that autoantibodies such as ACPA can appear up to two decades before rheumatoid arthritis manifests clinically (Fig. 19.5.3). Furthermore, affinity maturation and class-switching of these autoantibodies develops in the years immediately prior to disease onset. During the same period, pro-inflammatory cytokines and chemokines start to appear in peripheral blood, and C-reactive protein (CRP) levels rise. This prodromal period of serological abnormality has been termed 'pre-RA'. These observations have led to a model of rheumatoid arthritis aetiology, endorsed by the European League Against Rheumatism IgM-RF or anti-CCP anti-CCP IgM-RF 60 50 40 30 20 10 0 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 Year before the start of symptoms Percentage of positive patients 27.8% 40.5% 49.4% Fig. 19.5.3 Development of rheumatoid factor (RhF) and ACPA can precede the clinical onset of rheumatoid arthritis by many years. Reprinted from Arthritis & Rheumatism, volume 50, Nielen et al, pages 380–386. Copyright 2004 by the American College of Rheumatology, with permission from Wiley.

19.5 Rheumatoid arthritis 4419 (EULAR), whereby genetic and environmental risk factors combine to trigger a state of immune dysregulation termed 'systemic autoimmunity associated with rheumatoid arthritis'. After several years, and possibly additional triggers, a threshold is crossed after which the individual manifests symptoms and signs of rheumatoid arthritis. This may initially be symptoms without clinical arthritis, subsequently developing into unclassified arthritis and finally fulfilment of rheumatoid arthritis clinical classification criteria (Fig. 19.5.4). In this model distinct genetic and environmental factors, potentially influencing different immunopathological pathways, culminate in a final common clinical presentation of rheumatoid arthritis. The study of pre-rheumatoid arthritis is also revealing other relevant insights. For example, there is a high incidence of subclinical lung disease of varying types in these individuals. Combined with emerging microbiome data, and periodontitis as a risk factor, this highlights the likely importance of the mucosae as sites of tolerance breach in rheumatoid arthritis. Importantly this model is based largely upon studies of ACPA+ RA. Seronegative rheumatoid arthritis has a distinct and less well defined genetic and environmental predisposition, suggesting these to be different diseases with a

common phenotype. Epidemiology Rheumatoid arthritis has a global prevalence of approximately 1 in 400 and is around 2.5 times more common in women than men. The reported incidence varies widely between studies, and lies approximately between 20 and 50 per 100 000 per year in North America and Northern Europe and increases with advancing age. There is geographical variation in rheumatoid arthritis prevalence and incidence rates, although there is a paucity of data from developing countries. Rheumatoid arthritis is a significant cause of disability, mortality, and work-related absence, all of which contribute to the high economic impact of the disease. Prevalence The most recent and comprehensive rheumatoid arthritis prevalence data come from the 2010 Global Burden of Disease study, which found a global prevalence of 0.35% in females and 0.13% in males. Considerable geographic variation was found (Table 19.5.2), with notably lower prevalence in African regions. However, a lack of epidemiological data from developing countries, combined with underdiagnosis due to limited healthcare resources, is likely to have contributed to an underestimated prevalence in these regions. In contrast, several studies in developed Western countries estimate a prevalence of rheumatoid arthritis between 0.5 and 1% of the adult population. Several studies have also explored ethnic differences in rheumatoid arthritis prevalence; for example, a very high prevalence (5.3%) has been reported for the Pima and Papago Indians of Arizona, whereas lower rates have been observed in rural Chinese, Japanese, and African populations. These observed differences likely reflect a combination of both genetic and environmental risk factors. Incidence Of the few studies which have explored the incidence of rheumatoid arthritis, most have been conducted in retrospective cohorts in the United States and Europe. These studies suggest an annual incidence of between 20 and 50 per 100 000 adults—the wide range in part reflecting methodological variation (Table 19.5.3). Although the prevalence of rheumatoid arthritis has remained relatively stable, there is some evidence from longitudinal cohort studies for a decline in incidence over the past few decades. For example, an inception cohort study based in Rochester (USA) demonstrated a halving of annual incidence in women from 83 per 100 000 in 1955–1964 to 40 per 100 000 in 1985–1994. Several theories have been proposed to explain this observation, including a potential protective effect of the oral contraceptive pill. Gender and age In keeping with most autoimmune diseases, rheumatoid arthritis is more common in women with a female:male ratio of around 2.5:1. Although this finding is consistent in all populations, the underlying mechanisms remain unclear and could reflect hormonal factors and/or neoantigen exposure during pregnancy and breastfeeding. The onset of inflammatory arthritis in a child under the age of 16 years is, by definition, diagnosed as juvenile idiopathic arthritis. Notwithstanding this semantic limitation, the onset of rheumatoid arthritis can occur at any age, leading to an increasing prevalence with advancing age (Fig. 19.5.5). The peak age of onset is around the sixth decade for women and seventh decade for men. There is Genotype HLA-DRB1 PTPN22 CTLA4 STAT4 TRAF1–C5 PADI4 FCRL3 OLIG3–AIP3 TNF–AIP3 Tolerance breakdown Biomarkers: ACPA and rheumatoid factor Subclinical inflammation Biomarkers: ↑CRP, circulating cytokines and chemokines Additional environmental factors: Infection? Trauma? Stress? Inevitable progression? ≤ 5 years May take up to 15 years Mediterranean diet Anti-oxidants Alcohol? Oestrogens? Synovitis in single or multiple joints Biomarkers: subclinical synovitis in other joints (arthroscopy and imaging) Smoking Caffeine? Obesity? Fig. 19.5.4 Proposed model of rheumatoid arthritis aetiology. Individuals who are genetically predisposed towards developing rheumatoid arthritis encounter environmental insults which result in a loss of self-tolerance. The ensuing immune dysregulation leads to the production of autoantibodies and chronic subclinical inflammation which, after several years and in combination with possible further environmental insults, leads to the evolution of clinical disease. Reprinted by permission from Macmillan

section 19 Rheumatological disorders 4420 Table 19.5.2 Global prevalence and DALYs for rheumatoid arthritis in the age range 5–100 years, by region and sex, GBD 2010 study Age (standardized) All ages (thousands) Prevalence LCL UCL Region Sex % % % DALYs LCL UCL Global Male 0.13 0.12 0.13 1201 927 1538 Female 0.35 0.34 0.37 3618 2721 4602 Asia, central Male 0.16 0.12 0.21 17 12 23 Female 0.39 0.30 0.53 47 32 65 Asia, east Male 0.08 0.08 0.09 222 167 297 Female 0.24 0.22 0.27 601 446 779 Asia Pacific, high income Male 0.22 0.18 0.26 62 45 84 Female 0.57 0.48 0.69 229 162 307 Asia, south Male 0.08 0.07 0.09 212 130 291 Female 0.26 0.24 0.29 445 317 583 Asia, southeast Male 0.08 0.07 0.09 68 51 87 Female 0.23 0.21 0.26 186 136 242 Australasia Male 0.26 0.15 0.46 9 5 16 Female 0.66 0.37 1.11 31 18 53 Caribbean Male 0.15 0.12 0.18 7 5 9 Female 0.39 0.32 0.49 24 17 33 Europe, central Male 0.15 0.11 0.19 24 16 33 Female 0.41 0.31 0.52 95 63 133 Europe, eastern Male 0.14 0.08 0.22 43 28 64 Female 0.38 0.24 0.57 177 113 265 Europe, western Male 0.24 0.21 0.28 148 107 197 Female 0.63 0.55 0.75 548 382 734 Latin America., Andean Male 0.15 0.10 0.22 8 5 12 Female 0.39 0.25 0.59 27 18 42 Latin America, central Male 0.14 0.12 0.17 38 28 52 Female 0.40 0.34 0.49 138 101 180 Latin America, southern Male 0.20 0.13 0.30 14 9 21 Female 0.51 0.33 0.78 51 31 83 Latin America, tropical Male 0.14 0.13 0.15 27 20 36 Female 0.38 0.35 0.41 105 76 135 North Africa Middle East Male 0.09 0.08 0.11 42 30 55 Female 0.24 0.20 0.28 121 86 163 North America, high income Male 0.24 0.22 0.27 107 78 141 Female 0.63 0.58 0.70 388 285 503 Oceania Male 0.09 0.05 0.14 0.9 0.6 1 Female 0.25 0.15 0.41 2 1 4 Sub-Saharan Africa, central Male 0.12 0.07 0.18 12 6 22 Female 0.30 0.19 0.47 30 17 50 Sub-Saharan Africa, east Male 0.11 0.08 0.14 92 46 209 Female 0.29 0.23 0.37 232 152 433 Sub-Saharan Africa, south Male 0.10 0.09 0.12 9 7 12 Female 0.30 0.26 0.34 28 21 36 Sub-Saharan Africa., west Male 0.10 0.09 0.12 38 24 67 Female 0.28 0.25 0.32 112 81 164 DALYs, disability adjusted life years; GBD, Global Burden of Disease; LCL, lower confidence limit; UCL, upper confidence limit. Data from the 2010 Global Burden of Disease study, reproduced from: Annals of the Rheumatic Diseases, Cross et al, volume 73, pages 1316–22, copyright 2014 with permission from BMJ Publishing Group Ltd.

4421 Prevalence 0.030 0.025 0.020 0.015 0.010 0.005 0.000 0 20 40 60 80 100 Posterior rheumatoid arthritis prevalence female 2010 Age Posterior rheumatoid arthritis prevalence male 2010 Prevalence 0.030 0.025 0.020 0.015 0.010 0.005 0.0000 20 40 60 80 100 Age Sub-Saharan Africa, West Sub-Saharan Africa, Southern Sub-Saharan Africa, East Sub-Saharan Africa, Central North America, High Income North Africa/Middle East Oceania Asia, East Asia, Central Asia Pacific, High income Australasia Asia, South Caribbean Asia, Southeast Europe, Western Europe, Eastern Europe, Central Latin America, Southern Latin America, Tropical Latin America, Central Latin America, Andean Fig. 19.5.5 Worldwide prevalence of rheumatoid arthritis according to age. Reproduced from: Annals of the Rheumatic Diseases, Cross et al, volume 73, pages 1316–1322, copyright 2014 with permission from BMJ Publishing Group Ltd. Table 19.5.3 Estimates of annual incidence of rheumatoid arthritis by several studies Publication Country Type of study Incidence (cases/103 inhabitants) Population Age (years) Total Male Female Doran 2002 USA Retrospective 0.5 0.3 0.6 ≥18 Savolainen 2003 Finland Prospective 0.4a 0.3 0.5 ≥16 Chan 1993 USA Retrospective 0.3 0.2 0.5 ≥18 Kaipiainen-Seppanen 2000 Finland Retrospective 0.3a 0.2 0.4 ≥16 Riise 2000 Norway Retrospective 0.3a 0.2 0.4 ≥20 Uhlig 1998 Norway Retrospective 0.3 0.1 0.4 20–79 Kaipiainen-Seppanen 2001 Finland Retrospective 0.3 0.2 0.4 ≥16 Drosos 1997 Greece

Retrospective 0.2 0.1 0.4 ≥ 16 Symmons 1994 England Prospective 0.2 0.1 0.3 ≥ 16 Soderlin 2002 Sweden Prospective 0.2 0.2 0.3 ≥ 16 Guillemin 1994 France Retrospective 0.1 0.1 0.1 20–70 a Crude rates. Reprinted from Seminars in Arthritis and Rheumatism, volume 36, Alamanos et al, Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review, pages 182–188. Copyright (2006), with permission from Elsevier.

section 19 Rheumatological disorders 4422 some evidence to suggest a modern trend towards an advancing age of onset. Disability The capacity for rheumatoid arthritis to erode joints, alongside systemic features such as fatigue, makes rheumatoid arthritis an important cause of disability. In the 2010 Global Burden of Disease study, rheumatoid arthritis was the forty-second highest cause of disability of 291 conditions (falling between malaria and iodine deficiency) and was the cause of an estimated 3.7 million years lived with disability worldwide in 2010. Recent decades have witnessed a steady fall in the rates of joint damage, orthopaedic interventions, and long-term disability, consistent with improved treatment strategies implemented earlier in the disease course. Nevertheless, there remains an inverse relationship between average rheumatoid arthritis disease activity and national gross domestic product, suggesting the highest burden of disease among those patients with rheumatoid arthritis living in poorer countries (Fig. 19.5.6). Mortality Numerous studies have found a substantial increase in standardized mortality rates of around 1.2- to 3-fold in rheumatoid arthritis patients. Whereas mortality within the general population of developed countries has fallen sharply over the past six decades, the mortality of rheumatoid arthritis patients has only modestly reduced, leading to a further widening of this ‘mortality gap’ (Fig. 19.5.7). Life expectancy is reduced in severe rheumatoid arthritis by between 6 and 10 years although there is evidence to suggest a modest improvement over the past decade, consistent with reductions in joint damage and disability. The commonest causes of death in patients with rheumatoid arthritis reflect those in the general population, namely cardiovascular disease (especially myocardial infarction and heart failure), pulmonary disease (especially chronic obstructive pulmonary disease), infection, and cancer. The first three of these occur at a greater frequency in patients with rheumatoid arthritis, often with unusual presentations or greater severity. For example, patients with rheumatoid arthritis are more likely to suffer a sudden cardiac death or silent myocardial infarction compared with the general population. Overall cancer rates are similar between rheumatoid arthritis patients and the general population, but this statistic masks important differences. The risk of lymphoma, particularly non-Hodgkin B-cell subtypes, is significantly increased in patients with rheumatoid arthritis. Lung cancer is also around twice as common, potentially explained by the presence of smoking as a rheumatoid arthritis risk factor. In contrast the incidence of colorectal cancer is modestly reduced in patients with rheumatoid arthritis, which has 7.0 Ko Se Li La Hu Es It Ge UKSw USA De Ir Ne Fi Fr Sp Gr Po 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 0 5 10 15 20 25 30 GDP per capita, 1000€ DAS28 35 40 45 50 55 Fig. 19.5.6 Association between gross domestic product per capita (GDP) and disease activity score in 28 joints (DAS28) in 18 European countries and the United States in the QUEST-RA study. The correlation of GDP with DAS28 is $r = 20.85$ (95% CI 20.63–20.94); indicated with colour. The area of the disc is proportional to the total national health expenditure of each country in 2004. De, Denmark; Es, Estonia; Fi, Finland; Fr, France; Ge, Germany; Gr, Greece; Hu, Hungary; Ir, Ireland; It, Italy; Ko, Kosovo; La, Latvia; Li, Lithuania; Ne, The Netherlands; Po, Poland; Se, Serbia; Sp, Spain; Sw, Sweden. Reproduced from Annals of the Rheumatic Diseases, Sokka et al, volume 68, pages 1666–1672, copyright 2009 with permission from BMJ Publishing Group Ltd. 5 4 3 2 1 0 1970 1980

Calendar year 1990 2000 Mortality rate (per 100 py) 1970 1980 Calendar year 1990 2000 5 4 3 2 1 0 Mortality rate (per 100 py) Fig. 19.5.7 The mortality gap in rheumatoid arthritis. Observed mortality rates (solid line) in female patients with rheumatoid arthritis (top) and male patients with rheumatoid arthritis (bottom) and expected mortality rates (broken line) from the Minnesota white population, over the last 4–5 decades. Shaded areas indicate the 95% confidence limits for the observed mortality. Values are expressed per 100 person-years (py). Reprinted from *Arthritis & Rheumatism*, volume 56, Gonzalez et al, pages 3583–3587.

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19.5 Rheumatoid arthritis 4423 been attributed to the use of NSAIDs. Prostatic and female genital cancer may also be lower in rheumatoid arthritis, potentially for similar reasons. Economic impact Rheumatoid arthritis poses substantial direct costs to healthcare systems in terms of investigation, drug treatment, safety monitoring, and both outpatient and inpatient episodes. However, rheumatoid arthritis also carries very significant indirect costs including lost and reduced productivity due to sick leave and disability, welfare support, and the cost of providing social care. Poorly controlled rheumatoid arthritis substantially reduces quality of life, and also has a profound effect upon the lives of family members, friends, and carers. The economic impact of rheumatoid arthritis is therefore considerably greater than the direct healthcare costs alone. For example, in 2009 the United Kingdom National Audit Office estimated that the national direct healthcare cost of rheumatoid arthritis was £560 million; in the same year, the National Institute for Health and Care Excellence (NICE) estimated that the combined direct and indirect costs of rheumatoid arthritis were between £3.8 and £4.75 billion. Nevertheless, the wider economic impact of rheumatoid arthritis varies between countries dependent on different healthcare and social factors (Fig. 19.5.8). Thus evaluations of the cost-effectiveness of treatment strategies must take into account both direct and indirect costs specific to the healthcare system in which they will be delivered.

Pathogenesis The complex immune dysregulation present in the years before onset of symptoms makes it difficult to disentangle the order and relative importance of pathogenic events in the development of rheumatoid arthritis. Most immune cells have been implicated in rheumatoid arthritis pathogenesis, ranging from T and B lymphocytes of the adaptive immune system through to macrophages and dendritic cells of the innate immune system. Furthermore, resident cells within the joint including macrophages (type A synoviocytes), fibroblasts (type B synoviocytes), and osteoclasts each play important roles in articular damage and perpetuation of inflammation. Although some aspects of rheumatoid arthritis pathogenesis are relatively well understood, less is known about seronegative disease and less still about extra-articular inflammation. Indeed, it is becoming clear that rheumatoid arthritis is a heterogeneous condition, with various pathological pathways that may vary both between individuals as well as over time in the same patient.

The rheumatoid joint The defining macroscopic feature of active rheumatoid arthritis within the joint is the pannus—a potent mix of inflammatory cells, fibroblasts, and granulation tissue that destructively spreads throughout and beyond the joint. Macroscopically, the normally thin and translucent synovial membrane becomes extensively thickened and hypervascular, with undulating villous folds protruding into the joint space (Fig. 19.5.9). Accompanying this is an increased production of synovial fluid, leading to the characteristic joint effusion observed clinically. Beneath the pannus, destruction of cartilage and subchondral bone leads to radiological joint erosions, and invasion of pannus into surrounding structures causes tendon and ligament weakening and rupture. Synovium lining tendon sheaths can undergo similar changes. Microscopically within the pannus, there is hyperplasia of type B synoviocytes mixed with an

inflammatory infiltrate that includes USA 25 000 20 000 15 000 10 000 5000 0 Annual cost in (€)
 France Germany Italy Spain UK 3842 3422 7425 2974 4431 7224 4450 3031 1931 1138 1989 2506
 806 352 4900 4130 6114 2166 2230 1160 6041 3463 6476 702 6417 11 424 5127 1484 4411
 2029 Indirect costs Informal care Nonmedical costs Other medical costs Drug costs Fig. 19.5.8
 Annual per-patient direct and indirect costs of rheumatoid arthritis to the economies of five
 European countries and the United States. Reproduced from Furneri et al (2012). *Clinical and
 Experimental Rheumatology*; 30 (Suppl 73): S72–S84.

section 19 Rheumatological disorders 4424 macrophages, B and T lymphocytes, plasma cells, and dendritic cells. In contrast, the synovial fluid contains an abundance of neu- trophils. Sometimes the infiltrate is organized into lymphoid fol- licles, akin to those found in lymph nodes—so-called ectopic or tertiary lymphoid follicles. The extracellular matrix of articular car- tilage is digested by secreted lysosomal acid and enzymes such as the matrix metalloproteinases, with chondrocyte apoptosis and loss of cartilage architecture progressing to wholesale cartilage break- down. At the ‘leading edge’ of pannus, activation of osteoclasts results in peri-articular thinning of osteoid matrix and increased resorption of subchondral bone, with the development of ‘erosions’ visible on X-rays. The diverse mixture of cells within the pannus contributes to its potent destructive power. Although the precise order of events is difficult to identify, the key factors underpinning rheumatoid arthritis pathogenesis can be pragmatically divided into those of the adaptive and innate immune systems, and of the joint stroma. Adaptive immunity and rheumatoid arthritis pathogenesis CD4+ T lymphocytes Central to the pathogenesis of rheumatoid arthritis is the CD4+ T lymphocyte. These cells initiate and orchestrate adaptive immune responses via recognition of (auto)antigen on the surface of APCs. The importance of CD4+ T cells in rheumatoid arthritis patho- genesis is underscored by the strong association between rheuma- toid arthritis and the shared epitope, and by the high number of rheumatoid arthritis-associated SNPs within genes important for CD4+ T-cell function. Furthermore, many of these overlap with regions of epigenetic modification in CD4+ T cells, implying gene activation. CD4+ T cells release cytokines which determine the nature of the ensuing immune response. IL-17, produced by Th17 T cells, is a potent pro-inflammatory cytokine which can activate endothelial cells to enhance leucocyte recruitment, as well as activating syn- ovial fibroblasts and osteoclasts. Th17 cells are thought to play an important role in rheumatoid arthritis pathogenesis, counterbal- anced by regulatory T cells (Tregs). There are several types of regu- latory T cell which develop either in the thymus or, in the presence of anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF β), in noninflamed peripheral tissues and the gut. Tregs suppress immune responses and play an important role in the maintenance of self-tolerance. The balance of Tregs and pro- inflammatory T cell subsets is disrupted in several autoimmune dis- eases; in rheumatoid arthritis, there is evidence for both qualitative and quantitative Treg defects. CD4+ T cells also play a crucial role in the activation and mat- uration of B cells. So-called T follicular helper (TFH) cells are characterized by their expression of high levels of CXCR5 and production of IL-21. They are found in lymphoid follicles, and in synovial tissue and peripheral blood of rheumatoid arthritis pa- tients. T follicular regulatory (TFR) cells have also been recently characterized and may be important in the maintenance of per- ipheral tolerance. B lymphocytes and plasma cells The presence of autoantibodies in the serum of many rheumatoid arthritis patients suggests a role for B lymphocytes and plasma cells in rheumatoid arthritis pathogenesis. Indeed, the presence of rheumatoid factor (RhF) and ACPA many years prior to the symp- tomatic onset of rheumatoid arthritis suggests a possible role for these cells at an early disease stage. Furthermore, depletion of

B cells has therapeutic efficacy in established rheumatoid arthritis, suggesting the continued importance of this cell type in driving the autoinflammatory process. However, up to 30% of rheumatoid arthritis patients are seronegative and a pathogenic role for auto- antibodies has not been conclusively demonstrated. In addition to autoantibody production, B cells are potent APCs and, like T cells, secrete cytokines to drive and polarize the immune response. Recent (a) (b) Fig. 19.5.9 Macroscopic appearance of normal (a) and inflamed (b) synovium. Normal synovium is translucent, revealing underlying blood vessels; the inflamed synovium shows villus formation, increased vascularity, and fibrin deposition. Images courtesy of Dr. R Reece and Dr. J. Canete. Reproduced with permission from Isaacs JD, Moreland LW. Fast Facts: Rheumatoid Arthritis, 2nd edn. Oxford: Health Press Limited, 2011, fastfacts.com.

19.5 Rheumatoid arthritis 4425 interest has focused on regulatory B cells which, analogous to Tregs, have immunoregulatory functions. Innate immunity and rheumatoid arthritis pathogenesis

Macrophages Macrophages are cells of the innate immune system and are activated through pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) via intracellular and cell-surface receptors such as the Toll-like receptor (TLR) family. Macrophages can release large amounts of lysosomal enzymes, pro-inflammatory cytokines, and vasoactive compounds. Furthermore, they efficiently present antigen to CD4+ T cells, which in turn provide reciprocal stimulation to macrophages through direct cell contact and cytokines such as IL-1, IL-15, and TNF α . Macrophages are one of the first cells to enter a rheumatoid joint and their number provides a good correlate of rheumatoid arthritis disease activity, presumably in part via secretion of TNF α and IL-6. Although macrophages are thought to play a key role in rheumatoid arthritis pathogenesis, other innate immune cells are also present in the pannus. These include mast cells, which release vasoactive compounds that further enhance inflammatory cell recruitment, and natural killer cells.

Dendritic cells Dendritic cells (DCs) are often described as the sentinels of the immune system. They circulate through peripheral tissues and sample (auto)antigens while receiving environmental cues before entering lymph nodes, where they initiate either an activating or tolerogenic immune response. Furthermore the cytokines they secrete, such as IL-12 (pro-TH1) and IL-23 (pro-TH17), further polarize the ensuing immune response. Thus DCs have the potential to play a critical role in rheumatoid arthritis pathogenesis. They are present in synovial fluid and synovium of rheumatoid arthritis patients, and DCs isolated from rheumatoid arthritis joints activate CD4+ T cells in vitro. Costimulation blockade acts by inhibiting the interaction between APCs and T cells, and provides an effective biological treatment approach for rheumatoid arthritis.

Cytokines Numerous cytokines are produced by innate and adaptive immune cells within the rheumatoid arthritis synovium. Pro-inflammatory cytokines activate effector cells such as macrophages and osteoclasts, as well as upregulating vascular adhesion molecule expression. In concert with chemokines, which are essentially chemo-attractive cytokines, this increases cellular traffic into the joint. Cytokines also have important systemic effects such as induction of fatigue, upregulation of the acute-phase response and the anaemia of chronic disease. In health, pro-inflammatory cytokines are held in check by anti-inflammatory cytokines such as IL-10, as well as by soluble cytokine receptors and molecules such as the IL-1 receptor antagonist. Several pro-inflammatory cytokines including TNF α , IL-1, IL-6, and IL-17 have been therapeutically targeted by biological drugs in rheumatoid arthritis. While both TNF α and IL-6 blockade are highly efficacious, IL-1 blockade is less so. Similarly, despite the apparent importance of IL-17 in rheumatoid arthritis pathogenesis, blockade of this cytokine provides relatively modest benefits. Within one individual it is possible to observe a dramatic response to the blockade of one cytokine pathway, whereas

blockade of another is ineffective. Furthermore the benefits of cytokine blockade often wane over time, highlighting both redundancy and plasticity within the pathogenic cytokine pathways in rheumatoid arthritis. Joint stromal cells in rheumatoid arthritis pathogenesis Synoviocytes In rheumatoid arthritis pannus type B synoviocytes, also known as fibroblast-like synoviocytes (FLS), lose their normal physiological characteristics and produce pro-inflammatory cytokines and chemokines, as well as large amounts of destructive enzymes. Furthermore, increased cell turnover and a resistance to apoptosis confer quasi-malignant properties upon RA FLS, which directly invade and destroy adjacent joint tissues. They upregulate oncogenes, and experimental grafting of rheumatoid arthritis pannus into immune-deficient mice has demonstrated their ability to migrate via the vasculature, potentially 'spreading' synovitis from joint to joint, although whether this occurs in rheumatoid arthritis is unknown. While the events that lead to this transformation of FLS phenotype remain unclear, epigenetic modification likely plays an important role. Thus FLS maintain their pro-inflammatory phenotype ex vivo even after several cell cycles, supported by altered DNA methylation and microRNA regulatory networks. Such observations suggest that FLS help to perpetuate a state of chronic synovitis and represent an important therapeutic target. Osteoclasts Osteoclast activation is increased in the inflamed rheumatoid arthritis joint, secondary to up-regulated RANK-L expression by osteoblasts, FLS, and some inflammatory cells such as Th17 cells. Osteoclast differentiation from haematopoietic progenitors is also driven directly by cytokines such as TNF α . Increased osteoclast activity leads to peri-articular osteoporosis and bone resorption at the osteochondral junction. Impaired osteocyte function may also contribute to bone destruction. Pathogenesis of extra-articular manifestations of rheumatoid arthritis Rheumatoid arthritis is a systemic autoimmune disorder and substantial levels of inflammation occur outside of the joints. This causes organ damage and the multiple extra-articular manifestations discussed in the next section. One of the most characteristic features of extra-articular rheumatoid arthritis is the rheumatoid nodule, which usually occurs under the skin overlying bony prominences, or in viscera such as the lungs and heart. At the centre of a rheumatoid nodule is a focus of fibrinoid necrosis, which is surrounded by macrophages. Generalized and profound fatigue is a very common and disabling symptom of rheumatoid arthritis. In addition to psychological and social contributing factors, biological mechanisms also contribute. Activation of the HPA axis is a physiological adaptation to acute stresses such as infection or physical injury. In rheumatoid arthritis, however, chronic inflammation and sustained high levels of circulating inflammatory cytokines can cause dysfunction

section 19 Rheumatological disorders 4426 of both the HPA and hypothalamo-pituitary-gonadal (HPG) axes, which may in turn contribute to development of chronic fatigue and mood disorders. Circulating cytokines such as TNF α and IL-6 also undoubtedly contribute, but in some patients fatigue persists even when their joint disease is in remission. Clinical features Rheumatoid arthritis typically presents insidiously, although less common variants include acute, palindromic, polymyalgic, and systemic onsets. The principal feature of rheumatoid arthritis is an inflammatory arthritis which can affect any synovial joint, but typically involves the small joints of the hands, wrists, and feet in a symmetrical pattern. Patients describe episodic pain, stiffness, and swelling in affected joints, with joint stiffness usually worse in the mornings and after resting. There are also many extra-articular manifestations, which tend to be more common in patients with seropositive disease. Onset In most cases rheumatoid arthritis presents as a slowly progressive symmetrical arthritis affecting the small joints of the hands and feet. The insidious onset often results in delayed presentation to a family doctor or rheumatologist. In contrast, in some patients the onset can be

dramatic over just a few days, although this is less common. A smaller number of patients experience arthritis limited to just a few joints, which can be asymmetrical and transient, moving from joint to joint in a pattern termed 'palindromic rheumatism'. Patients with palindromic rheumatism are often asymptomatic between bouts of arthritis, although with time can progress to a more classical rheumatoid arthritis phenotype. Around 10% of patients present with a polymyalgic onset of rheumatoid arthritis, where the onset of arthritis is accompanied or even preceded by proximal myalgia, stiffness, and fatigue. Polymyalgic rheumatoid arthritis is rarely observed in patients under the age of 60 years. Finally, rheumatoid arthritis can occasionally present as a systemic illness with extra-articular features dominating. Such systemic presentations are fortunately rare and warrant careful exclusion of alternative diagnoses such as adult-onset Still's disease, other autoimmune connective tissue diseases such as systemic lupus erythematosus, and malignancy.

Articular features Pattern of arthritis Rheumatoid arthritis can affect any synovial joint, although most frequently starts in the small joints of the hands and feet. The metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP) and wrist joints are commonly affected, whereas distal interphalangeal joint arthritis is not characteristic and should raise the suspicion of psoriatic arthritis or osteoarthritis. The elbows, knees, ankles, and shoulders are also commonly involved, whereas the temporomandibular and sternoclavicular joints are less commonly affected. Whereas cervical spine involvement is relatively common, thoracolumbar spine and hip joint inflammation is rare in rheumatoid arthritis and their presence should prompt a consideration of alternative diagnoses.

Symptoms of arthritis Patients with rheumatoid arthritis typically describe a deep 'toothache-like' pain in affected joints, which is accompanied by a disabling stiffness that is worse in the mornings and after rest. The duration of early morning stiffness after waking is a useful measure of disease activity. Indeed, an important diagnostic feature of the pain and stiffness of rheumatoid arthritis is their relief by activity and aggravation by rest, in contrast to osteoarthritis. The activity of rheumatoid arthritis tends to wax and wane, with flares of arthritis that develop over days but which can take weeks to subside. Such flares are often unpredictable but can be triggered by emotional distress and physiological insults such as infection or surgery.

Physical signs of arthritis The visible extent of arthritis depends both upon the duration of disease and its severity. In most patients with early rheumatoid arthritis, the only signs on examination are mild joint swelling and tenderness on palpation. A slight erythema may be present in the skin overlying the joint. Joint swelling in rheumatoid arthritis results from a combination of synovial thickening and synovial effusion, and is typically described as 'boggy' to palpation in contrast to the hard bony swelling of nodal osteoarthritis or the fluctuance of a large effusion. Lateral squeeze pressure applied gently across the MCP and MTP joints is a useful and sensitive screening technique for synovitis in these commonly affected joints. Only when synovitis has persisted for several months or longer do the hallmark joint deformities of rheumatoid arthritis start to develop. Typical deformities develop in the hands and feet secondary to joint and tendon subluxation and dislocation (Fig. 19.5.10 and Table 19.5.4). Tendon sheaths can also become inflamed (tenosynovitis) leading to painful triggering and locking of digits and, ultimately, tendon rupture. Destruction of articular cartilage and erosion of subchondral bone also leads to physical deformity and reduced range of movement at affected joints. The prevention of bone and cartilage damage, and consequent deformities, is a key aim of modern rheumatoid arthritis treatment strategies.

Extra-articular features Rheumatoid arthritis is associated with various extra-articular manifestations (Table 19.5.5), some common and others rare, but all contributing to the burden of morbidity. Extra-articular features often cluster, such that a patient with one extra-articular manifestation is more likely to develop others. Several of the commonest extra-articular features

contribute to the excess mortality of rheumatoid arthritis. The incidence of extra-articular features is greater in seropositive rheumatoid arthritis, as is joint destruction, thus making autoantibodies useful as both diagnostic and prognostic biomarkers. Cardiovascular Vasculitis occurs in around 3% of rheumatoid arthritis patients, an incidence that appears to be falling. Rheumatoid arthritis vasculitis

19.5 Rheumatoid arthritis 4427 is more common in men and is strongly associated with smoking, the presence of rheumatoid nodules and the presence of high titres of RhF. It typically affects small- and medium-sized vessels, and usually presents as vasculitic infarcts in the distal extremities, especially in the nail folds. In more severe cases necrotic ulcers can develop, usually on the lower legs, which are persistent and slow to (a) (b) (c) Fig. 19.5.10 Characteristic appearance of the hands and feet in long-standing rheumatoid arthritis. (a, b) The hands demonstrate: swelling, subluxation, and ulnar deviation at the metacarpophalangeal joints; flexion deformities of the fingers and Z deformity of the thumb on the right; and early swan neck deformities on the left. Multiple rheumatoid nodules are also evident, as is (teno)synovitis at the right wrist. (c) The feet demonstrate swelling and valgus deformities at the ankles, flattening of the longitudinal arches with pes planus, and early clawing of the toes. Reproduced with permission from Isaacs JD, Moreland LW. Fast Facts: Rheumatoid Arthritis, 2nd edn. Oxford: Health Press Limited, 2011, fastfacts.com. Table 19.5.4 Characteristic hand and wrist deformities in rheumatoid arthritis

Region	Physical sign	Fingers
Boutonnière deformity	(fixed flexion of PIPJ and hyperextension of DIPJ)	Swan neck deformity (fixed hyperextension of PIPJ and flexion of DIPJ)
Ulnar deviation	MCPJ palmar subluxation	Thumb Z-thumb deformity (fixed flexion of the first MCPJ and hyperextension of the IPJ)
Palm	Wastage of intrinsic hand musculature (esp. thenar eminence from median nerve compression in the carpal tunnel)	Palpable flexor tendon thickening and finger triggering
Wrist	Radial deviation	Prominent ulnar styloid process

DIPJ, distal interphalangeal joint; IPJ, interphalangeal joint; MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint. Table 19.5.5 The extra-articular features of rheumatoid arthritis

Organ system	Extra-articular manifestation
Cardiac	Pericarditis
Heart	block
Circulatory	Vasculitis
Pulmonary	Inflammatory interstitial lung disease
Pulmonary	fibrosis
Pulmonary	nodules
Pleural	effusion
Caplan's	syndrome
Neurological	Compression neuropathy (e.g. carpal tunnel syndrome)
Cervical	myelopathy (secondary to atlanto-axial subluxation or subaxial subluxation)
Peripheral	neuropathy
Ocular	Keratoconjunctivitis sicca
Scleritis	Scleromalacia perforans
Episcleritis	Peripheral ulcerative keratitis
Corneal	melt
Haematological	Anaemia
Thrombocytosis	Felty's syndrome
Lymphoma	
Dermatological	Rheumatoid nodules
Rheumatoid	neutrophilic dermatosis
Cutaneous	vasculitis and vasculitic ulcer
Pyoderma	gangrenosum
Constitutional	Fatigue
Anorexia	Weight loss
Osteoporosis	
Amyloidosis	

section 19 Rheumatological disorders 4428 heal. In the worst cases, a full-blown systemic vasculitis can occur resembling polyarteritis nodosa, although without microaneurysm formation. The treatment of rheumatoid vasculitis depends on its severity, although there is a poor evidence-base. Mild vasculitis with peripheral small infarcts often responds to optimization of traditional immunosuppressive therapy plus low-dose glucocorticoids, whereas systemic vasculitis with end-organ involvement may require cytotoxic treatment and high-dose glucocorticoids. Biological drugs such as rituximab may also have a place in the treatment of severe rheumatoid arthritis vasculitis. Rheumatoid arthritis may also be associated with the development of pericarditis and heart block (secondary to a rheumatoid nodule in the conducting system). Pulmonary The pulmonary

manifestations of rheumatoid arthritis have not reduced with modern management and make an important contribution to excess mortality. Subclinical abnormalities can be demonstrated by appropriate imaging in more than 50% of patients in some studies. Interstitial lung disease can be an extra-articular manifestation of rheumatoid arthritis as well as an adverse effect of medications such as methotrexate and leflunomide (Fig. 19.5.11). A variety of patterns of interstitial lung disease can be observed in rheumatoid arthritis, the most common of which is usual interstitial pneumonia (UIP) followed by nonspecific interstitial pneumonia (NSIP), although mixed disease and other patterns also occur. Rheumatoid nodules also occur in the lung, although these are usually asymptomatic and of clinical importance only due to the need to exclude malignancy. A particularly florid form of pulmonary rheumatoid nodulosis known as Caplan's syndrome is observed in the setting of pneumoconiosis, especially in male coal-miners. The incidence of this complication has fallen in recent decades, possibly due to better occupational health measures. Pleural inflammation can result in chronic pleural effusions, which are classically exudative and often recur after drainage unless systemic disease activity is adequately controlled. Neurological The most common neurological deficits in rheumatoid arthritis are secondary to compressive neuropathies as a consequence of synovitis and bony deformities. Particularly vulnerable to compression are the median nerve as it traverses the carpal tunnel at the wrist, and the ulnar nerve as it passes around the lateral epicondyle of the elbow and through Guyon's canal at the wrist. Nerve palsies may occasionally be seen as a result of mononeuritis multiplex in patients with rheumatoid vasculitis. Persistent inflammation within the cervical spine can lead to instability, subluxation, and spinal cord compression. While subaxial disease is more common, instability of the atlanto-axial joint due to erosion or dislocation of the odontoid peg is a classical extra-articular manifestation of rheumatoid arthritis. If subluxation occurs, compression of the spinal cord can ensue (Fig. 19.5.12). Detection of cervical instability may require dynamic imaging, and surgical fixation is essential before the onset of neurological symptoms. Cervical subluxation tends to be observed in patients with established rheumatoid arthritis that has been poorly controlled and should always be considered prior to a general anaesthetic, with modification to intubation procedures as necessary for high risk patients. Ocular Keratoconjunctivitis sicca (dryness of the eyes) is a commonly observed feature of rheumatoid arthritis and may occur as part of a secondary Sjogren's syndrome. Ocular inflammation in rheumatoid arthritis tends to manifest as episcleritis, scleritis, and peripheral ulcerative keratitis. Episcleritis typically presents as a painless 'gritty' red eye. In contrast, scleritis presents as a painful red eye which, if left untreated, can result in thinning of the sclera and perforation (Fig. 19.5.13). Dependent on the location of scleral involvement, its detection may require retraction of the eyelid and deviated gaze. Occasionally scleral necrosis develops in the absence of pain or apparent inflammation, a condition called scleromalacia perforans. Peripheral ulcerative keratitis is characterized by ulceration around the corneal limbus, which in severe cases results in 'corneal melt'. Scleritis and peripheral ulcerative keratitis are potentially sight-threatening and warrant urgent ophthalmological assessment and aggressive topical and systemic immunosuppression. Haematological Anaemia is a common finding in established rheumatoid arthritis and can be caused by a variety of factors (Table 19.5.6). The commonest is anaemia of chronic disease secondary to chronic systemic inflammation, which can also drive a thrombocytosis. An important mediator in both processes is IL-6, which stimulates megakaryocyte differentiation as well as stimulating hepatocytes to release hepcidin, which leads to iron sequestration and reduced Fig. 19.5.11 High-resolution computed tomography (HRCT) of interstitial lung disease in rheumatoid arthritis. A usual interstitial pneumonia (UIP) pattern is more prevalent in rheumatoid arthritis, with basal subpleural honeycombing on CT. Reproduced from

Watts RA et al (eds) Oxford Textbook of Rheumatology, 4th edn. Oxford University Press, 2013. By permission of Oxford University Press.

19.5 Rheumatoid arthritis 4429 absorption. Autoimmune haemolytic anaemia also occurs in rheumatoid arthritis, as do autoimmune thrombocytopenia and neutropenia. Felty's syndrome is the combination of rheumatoid arthritis, neutropenia and splenomegaly, and affects less than 1% of patients. The mechanisms underlying neutropenia are incompletely understood, but may include both reduced production and immune-mediated increased peripheral (a) (b) (c)

Fig. 19.5.12 (a, b) Plain cervical spine radiographs of a patient with rheumatoid arthritis, demonstrating anterior subluxation of the atlas (C1) on flexion, with increased distance between the odontoid peg and anterior arch of the atlas. (c, d) The eroded and posteriorly migrated dens is clearly visible on sagittal and transverse CT scans. (e, f) Sagittal and transverse MRI scans demonstrate indentation of the spinal canal by inflammatory tissue at C1, as well as additional damage at the lower cervical levels. Images courtesy of Dr. G. Hide. Reproduced with permission from Isaacs JD, Moreland LW. Fast Facts: Rheumatoid Arthritis, 2nd edn. Oxford: Health Press Limited, 2011, fastfacts.com. (d) (e) (f) Fig. 19.5.12 Continued

section 19 Rheumatological disorders 4430 consumption. The neutropenia of Felty's syndrome can reach clinically significant levels with bacterial infection. Rheumatoid arthritis patients are more likely to develop haematological malignancies, particularly B-cell non-Hodgkin's lymphoma and, to a lesser extent, multiple myeloma. Chronic inflammation may drive malignant transformation in lymphocytes, and the risk of lymphoma is greater in those patients with more active disease (Fig. 19.5.14). Dermatological There are several cutaneous manifestations of rheumatoid arthritis (Table 19.5.5). The best-known are rheumatoid nodules—firm and usually painless subcutaneous nodules which develop principally over the extensor surfaces of the elbows and fingers (Fig. 19.5.15). Rheumatoid nodules are almost exclusively found in patients with seropositive rheumatoid arthritis, and may occur alongside other extra-articular disease. They sometimes develop in the viscera, notably the lung (see previous section on the pulmonary system). Rheumatoid nodules are usually asymptomatic unless they become infected or cause mass-occupying effects, in which case they can be surgically excised. A nodule in the conducting system of the heart, however, can cause heart block. Adequate control of systemic inflammation usually reduces nodulosis although rapid acceleration has been observed upon treatment with methotrexate. In contrast, hydroxychloroquine may reduce nodulosis. Rheumatoid neutrophilic dermatosis (RND) is an uncommon condition characterized by erythematous papules, nodules, or plaques secondary to lymphocyte and neutrophil infiltration of the dermis. RND usually occurs in patients with established rheumatoid arthritis and principally affects the trunk and extensor aspects of the extremities such as the forearms and hands. Fig. 19.5.13 Scleromalacia perforans. A 50-year-old woman with severe rheumatoid arthritis has suffered from relapsing scleritis for over 20 years. She now has a very thin superior sclera with underlying choroid bulging through. Reproduced from Watts RA et al (eds). Oxford Textbook of Rheumatology, 4th edn. Oxford University Press, 2013. By permission of Oxford University Press. Table 19.5.6 Common causes of anaemia in rheumatoid arthritis. G6PD: glucose-6-phosphate dehydrogenase • Anaemia of chronic disease • Iatrogenic — Bone marrow suppression (e.g. methotrexate) — Haemolysis (e.g. sulfasalazine in G6PD deficiency) — Peptic ulcer disease and NSAID therapy • Autoimmune — Autoimmune haemolytic anaemia — Co-incidental pernicious anaemia • Haematinic deficiency (iron, folate, vitamin B12) Cases/Controls 0 5 1st 2nd 3rd 4th 5th 6th 7th 8th 9th 10th 10 15 20 OR

(95% c.i.) Cumulative disease activity decile 25 30 35 40 45 50 55 60 65 181 9/41 11/41 7/38 14/36 16/39 9/36 18/38 27/36 35/37 226/37 Fig. 19.5.14 Risk of lymphoma in relation to cumulative disease activity, assessed in 372 patients with lymphoma and rheumatoid arthritis, and in matched cancer-free rheumatoid arthritis controls. Symbols show unadjusted odds ratios (ORs); bars show 95% confidence intervals (95% CIs). Deciles of the area under the curve for cumulative disease activity are shown above each symbol; ORs were calculated using the first decile as the reference. A line is included where OR 1. Reprinted from *Arthritis & Rheumatism*, volume 54, Baecklund et al, pages 692–701. Copyright 2006 by the American College of Rheumatology, with permission from Wiley.

19.5 Rheumatoid arthritis 4431 Systemic features As a result of chronic, systemic inflammation patients with severe active rheumatoid arthritis may develop cachexia with anorexia, weight loss, profound fatigue, and depression. Systemic inflammation, in addition to glucocorticoids, is also associated with osteoporosis in rheumatoid arthritis patients. Many years of uncontrolled systemic inflammation can provoke amyloidosis with renal and cardiovascular pathology although this is now extremely rare.

Diagnosis Rheumatoid arthritis classification criteria Several rheumatoid arthritis classification criteria have been proposed over the past few decades. Historically these placed emphasis upon the development of features of established rheumatoid arthritis, such as joint erosions and rheumatoid nodules. These therefore performed poorly in the early disease stages, precisely when diagnosis is most important yet challenging. To address this paradox, the 2010 American College of Rheumatology (ACR) and EULAR classification criteria remove features of established rheumatoid arthritis and instead focus upon the number and nature of involved joints, serology, acute-phase reactants and symptom duration (Table 19.5.7). These criteria can be fulfilled cumulatively over time and generally have greater discrimination for early rheumatoid arthritis than previous classification systems. Nevertheless diagnosis can still be challenging, particularly in seronegative disease. While rheumatoid arthritis classification criteria have been invaluable for standardization in research there are no pathognomonic features, and all classification criteria require that there must not be a more likely alternative diagnosis for the patient's presentation. In practice therefore, rheumatoid arthritis remains firmly a clinical diagnosis based upon history, examination, and relevant investigations.

Differential diagnosis The differential diagnosis of rheumatoid arthritis is broad, owing to the many causes of arthralgia and arthritis. The onset, pattern, and nature of joint involvement can each provide useful clues towards the diagnosis, which may only manifest with the passage of time. The differential diagnosis of inflammatory arthritis according to clinical presentation is listed in Table 19.5.8.

Overlap syndromes Rheumatoid arthritis is associated with an increased risk of developing other autoimmune disorders. In some patients this results in an evolution of clinical phenotype with time. Thus rheumatoid arthritis patients may occasionally develop autoantibodies against nuclear antigens, followed by features of other connective tissue diseases such as Sjögren's syndrome or systemic lupus erythematosus. Similarly, patients with systemic lupus erythematosus can develop RhF and ACPA concurrent with onset of a rheumatoid arthritis pattern of synovitis, colloquially known as 'rhumus'. These observations highlight the dynamic nature of autoimmunity in rheumatoid arthritis and the need for the

Fig. 19.5.15 Patient with rheumatoid arthritis presenting with involvement of the elbow accompanied by effusion in the olecranon fossa and bursitis, plus a rheumatoid nodule distal to olecranon bursitis. Reproduced from Watts RA et al (eds). *Oxford Textbook of Rheumatology*, 4th edn. Oxford University Press, 2013. By permission of Oxford University Press.

Table 19.5.7 The 2010 American College of Rheumatology (ACR) and European

League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. Patients should have at least one joint with definite synovitis which is not better explained by another disease

Criterion Score A. Joint involvement a – 1 large joint – 2–10 large joints – 1–3 small joints (with or without involvement of large joints) – 4–10 small joints (with or without involvement of large joints) – >10 joints (at least one small joint) 1 2 3 4 5 B. Serologyb – Negative RhF and negative ACPA – Low-positive RhF or low-positive ACPA – High-positive RhF or high-positive ACPA 0 2 3 C. Acute-phase reactants – Normal CRP and normal ESR – Abnormal CRP or abnormal ESR 0 1 D. Duration of symptoms – <6 weeks – ≥6 weeks 0 1 ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; RhF, rheumatoid factor. A score of ≥6/10 is required for classification of a patient as having definite rheumatoid arthritis (criteria can be cumulatively fulfilled over time) a ‘Large joints’ refers to shoulders, elbows, hips, knees, and ankles. ‘Small joints’ refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists. The distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment b Negative refers to international unit (IU) values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where RhF information is only available as positive or negative, a positive result should be scored as low-positive for RhF. Reproduced from: *Annals of the Rheumatic Diseases*, Aletaha et al, volume 69, pages 1580–8, copyright 2010 with permission from BMJ Publishing Group Ltd.

section 19 Rheumatological disorders 4432 clinician to remain vigilant to change and prepared to revise the diagnosis and treatment approach where necessary. Clinical investigations The clinical investigations for a patient presenting with potential rheumatoid arthritis are presented in Table 19.5.9. Several investigations are included at baseline to aid the subsequent detection of extra-articular features or medication-related side effects, such as a chest radiograph and pulmonary function tests. Similarly, as atherosclerosis is accelerated in rheumatoid arthritis, cardiovascular risk profiling including blood pressure measurement, electrocardiogram, and lipid profile are also appropriate. Autoantibodies The first autoantibody to be characterized in rheumatoid arthritis was RhF, an autoantibody directed against the Fc portion of the immunoglobulin (Ig) G molecule. Although RhF can exist in any isotype, it is the IgM isotype which is most well-known and clinically utilized. IgM RhF forms pentameric complexes with IgG, and is a potent activator of complement. More recently, several other classes of autoantibody have been discovered in rheumatoid arthritis, of which ACPA testing is now in widespread clinical use. Together with the recently characterized anti-carbamylated peptide autoantibodies, these emphasize the importance of post-translationally modified peptides as potential autoantigens in rheumatoid arthritis. Testing for the presence of RhF and ACPA can be useful diagnostically, mainly where there is an intermediate clinical suspicion of rheumatoid arthritis. Where there is a high pre-test probability, autoantibody testing has limited diagnostic value as up to 35% of patients who satisfy rheumatoid arthritis classification criteria are seronegative for both RhF and ACPA. Furthermore, RhF has poor specificity for rheumatoid arthritis and can be elevated in a variety of circumstances, including other autoimmune conditions, chronic infections, as well as in otherwise healthy individuals. It is therefore of little diagnostic use in settings where the clinical suspicion of rheumatoid arthritis is low. In contrast the specificity of ACPA is high at around 95%, and hence a positive finding is usually indicative of rheumatoid arthritis in the appropriate clinical setting. Autoantibodies also carry

prognostic value in rheumatoid arthritis. Thus patients who are seropositive for RF and (particularly) ACPA are at increased risk of developing joint damage and extra-articular complications. Table 19.5.8 The differential diagnosis of rheumatoid arthritis according to typical clinical presentation, although overlap between presentations can exist

Clinical presentation	Differential diagnosis
Polyarthritis/ arthralgia	Polyarticular psoriatic arthritis, Polyarticular osteoarthritis, Haemochromatosis, Remitting seronegative symmetrical synovitis with pitting (o)edema (RS3PE), Connective tissue diseases (e.g. systemic lupus erythematosus), Sarcoidosis, Fibromyalgia, Systemic onset Adult-onset Still's disease, Polymyalgia rheumatica, Paraneoplastic syndrome
Numerous systemic infections, including:	– Parvovirus – Lyme disease – Human immunodeficiency virus seroconversion illness – Chikungunya fever – Dengue fever – Whipple's disease – Disseminated gonococcal infection
Mono- or oligo-arthritis/ arthralgia	Septic arthritis, Crystal arthropathy (gout, pseudogout), Haemarthrosis, Seronegative spondyloarthropathy – Psoriatic arthritis – Enteropathic arthritis – Reactive arthritis – Ankylosing spondylitis with peripheral joint involvement

Table 19.5.9 Typical investigations for a patient presenting with possible rheumatoid arthritis. Not all of these investigations would need to be performed in every case, and should be tailored to the history and examination

Category	Investigation
Biochemistry	C-reactive protein, Renal and liver function tests (baseline prior to drug therapy), Ferritin, Uric acid, Thyroid function tests, Calcium, phosphate, Angiotensin converting enzyme, Vitamin D
Haematology	Full blood count, Erythrocyte sedimentation rate
Serology	Rheumatoid factor, Anti-citrullinated peptide antibodies, Other autoantibodies as dictated by clinical picture (e.g. ANA, ENAs, ANCA, anti-cardiolipin antibody)
Infectious agent serology tests (if appropriate, e.g. ASO titre, parvovirus, hepatitis B and C, HIV, Lyme disease)	Immunoglobulins and serum protein electrophoresis
Synovial fluid analysis	Synovial fluid microscopy and culture (if septic arthritis suspected), Polarizing light microscopy (if crystal arthropathy suspected)
Imaging	Plain radiographs of hands and feet, Musculoskeletal ultrasonography (if available)
Other tests	Pulmonary function tests (baseline prior to e.g. methotrexate therapy), Chest X-ray, Cardiovascular risk profiling – Electrocardiography – Fasting lipid profile
Investigation of extra-articular features (when indicated)	Nerve conduction studies, HRCT of chest, Echocardiogram, ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ASO, anti-streptolysin O; ENAs, extractable nuclear antigens; HIV, human immunodeficiency virus; HRCT, high-resolution computed tomography.

19.5 Rheumatoid arthritis

4433 Musculoskeletal

imaging Plain radiographs

remain a useful tool for the

detection of joint erosions, particularly in the hands and feet. As well as providing prognostic information they can also help distinguish rheumatoid arthritis from other differential diagnoses such as psoriatic arthritis and crystal arthropathies. Nevertheless, apart from providing a baseline, plain radiographs have limited utility in early rheumatoid

arthritis, before joint damage has developed. Magnetic resonance imaging (MRI) is significantly more sensitive and can detect both synovial inflammation and the bone oedema that precedes erosions. While potentially of use in early rheumatoid arthritis, however, its cost and inconvenience due to slow scan times restricts its use

largely to research studies. Musculoskeletal ultrasound has gained popularity in recent years, and is regarded by many as the imaging modality of choice in rheumatoid arthritis. The relatively low cost and size of ultrasound equipment make it ideal for use in the clinic and at the bedside, and real-time imaging allows for dynamic assessment of

joint and tendon movement. Ultrasound can detect both synovial thickening and hypervascularity, together with joint effusions and articular erosions. It is of particular use as an addition to clinical examination in the detection of synovitis in early rheumatoid arthritis, but is also useful in the assessment of treatment response and in the guiding

of articular injections.

A further useful setting is the patient who is refractory to multiple medications, where ultrasound can help to distinguish active synovitis and joint damage from superadded fibromyalgia. Nevertheless, musculoskeletal ultrasound is operator- dependent and relies upon appropriate training and standardization

of equipment. Synovial fluid analysis The aspiration of synovial fluid from inflamed joints can provide both symptomatic relief and the opportunity to inject glucocorticoid. Although there are no features of synovial fluid which are specific for rheumatoid arthritis, synovial fluid analysis can be invaluable in the exclusion of differential

diagnoses. This includes microbial culture in suspected septic arthritis, and polarizing light microscopy for the diagnosis of crystal arthropathies.

Composite clinical disease activity scores Measurement of disease activity in rheumatoid arthritis has improved outcomes by enabling objective assessment of response to

treatment. No single measurement adequately captures all aspects of disease activity and consequently several composite scoring systems have been developed that encompass a range of different domains. The most well-known is the disease activity score in 28 joints (DAS28), a composite measure including joint

examination, patient subjective assessment and erythrocyte sedimentation rate (ESR) (Table 19.5.10). The DAS28 was derived from the original DAS, which assessed 44 joints, but DAS28 is similarly discriminative and much quicker to score in daily practice. An alternative version of DAS28 uses CRP instead of ESR. Other

composite scores include the simple disease activity index (SDAI), which is similar to DAS28 but easier to calculate and includes a physician global assessment, and the clinical disease activity index (CDAI), which does not require ESR or CRP and can therefore be calculated without laboratory results. There is increasing interest

in the use of patient-reported outcome measures (PROMs) in rheumatoid arthritis, both for the measurement of disease activity but also for other aspects of disease such as functional ability, fatigue, and quality of life. Use of such instruments can therefore provide a more global assessment of disease status. The Stanford

Health Assessment
Questionnaire (HAQ)
measures functional ability
and EuroQol 5 Dimensions
(EQ-5D) is a quality of life
instrument, both of which
are used in health economic
assessments by bodies
such as the National
Institute for Health and Care
Excellence (NICE). In
contrast, the Nottingham
Short Form 36 (SF36)

combines several features in physical and mental health domains and is commonly used to assess quality of life in clinical trials. The optimal disease state for a rheumatoid arthritis patient is remission. As with diagnostic criteria and disease activity measures, various definitions of remission have existed over recent decades and coexist

today. A commonly used definition in daily practice is a DAS28 of less than 2.6, although this does not exclude the potential to have residual synovitis, for example in the feet.

Recently, EULAR and the ACR developed new remission criteria (the 2011 ACR/EULAR remission criteria). These are more stringent than previous

criteria and require a patient to have no more than one tender or swollen joint, a $\text{CRP} \leq 10$ mg/litre, and a patient global assessment of 10 or less on a 100 point scale (Table 19.5.11). These are the so-called Boolean criteria but, as an alternative, an index-based definition of $\text{SDAI} \leq 3.3$ was also proposed and accepted.

Table 19.5.10 The disease

activity score in 28 joints (DAS28). The 28 joints assessed include the bilateral proximal interphalangeal, thumb interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, and knee joints. The DAS28 score can be used to define thresholds of disease activity, though it is widely recognized that DAS28 can underestimate

disease activity at and close
to remission levels DAS28
score Interpretation

DAS28 <2.6 Remission

$2.6 \leq \text{DAS28} \leq 3.2$ Low disease

activity $3.2 < \text{DAS28} \leq 5.1$

Moderate disease activity

$\text{DAS28} > 5.1$ High disease

activity ESR, erythrocyte

sedimentation rate in

mm/hour; SJC, swollen joint

count; TJC, tender joint

count; VASpatient, patient

visual analogue score of
general health ranging from
zero (best) to 100 (worst).

DAS TJC SJC ESR VAS 28

0.56 28 0.28 28 0.70 In

0.014 patient

•
× + × + × Table 19.5.11 The American College of Rheumatology (ACR)/ EULAR 2011 Boolean remission criteria for rheumatoid arthritis. For patient global assessment the following anchor statement is used: 'Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?' (anchors: very well-very poor) At any single time point, the patient must satisfy all of the following: Tender joint count ≤ 1 Swollen joint count ≤ 1 Patient global assessment ≤ 10 (on a 100-point scale) C-reactive protein ≤ 10 mg/litre Reproduced from: Annals of the Rheumatic Diseases, Felson et al, volume 70, pages 404-413, copyright 2011 with permission from BMJ Publishing Group Ltd.

section 19 Rheumatological disorders 4434 Treatment The past two decades have witnessed a revolution in rheumatoid arthritis outcomes, from a disease in which progressive deformity and disability were almost inevitable to one where remission is a realistic aim for many patients. This revolution has been underpinned by a paradigm shift in treatment, including the importance of early intervention before irreversible joint damage occurs; 'treatment-to-target', whereby therapy is escalated until a treatment target (such as DAS28 remission) is achieved; and the advent of several classes of potent, targeted biological and synthetic drugs. Nonetheless, it is also important to remember that a systemic immune disorder such as rheumatoid arthritis demands a holistic approach in which a multidisciplinary model remains central to patient care. The therapeutic 'window of opportunity' and treatment-to-target There is now considerable evidence that successful suppression of synovitis at an early stage results in better long-term rheumatoid arthritis outcomes. For example, data from the Leiden Early Arthritis Clinic show that patients treated within 12 weeks of symptom onset achieve better outcomes, regardless of the specific therapy. Outcomes measured included joint damage, disability, the cumulative likelihood of

achieving remission and even mortality. Other studies have shown that HAQ score, even during the first year of disease, reflects subsequent mortality. The reason why early treatment has such a dramatic effect on long-term outcomes is currently uncertain, but may reflect epigenetic consequences of inflammation, for example, in FLS and the cardiovascular system. The concept of a 'window of opportunity' has led to a paradigm shift in the treatment of rheumatoid arthritis. Historically, disease-modifying medications were introduced late and slowly escalated, often only after damage had appeared on X-rays. In contrast, current treatment strategies focus on the early initiation of medications, often in combination with local and systemic glucocorticoids, in order to rapidly and completely suppress synovitis. Many healthcare systems have introduced mechanisms of rapid access to rheumatologists, such as early arthritis clinics, to deal with these previously unrecognized medical emergencies. Alongside early intervention has arisen the treatment-to-target concept. Studies such as the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial demonstrated the long-term benefits of a step-down approach in which initial aggressive treatment with glucocorticoids and combination DMARDs led to rapid disease control followed by tapering of therapy. In contrast, the Tight Control for RA (TICORA) trial illustrated the importance of a treatment target, which was achieved by regular (e.g. monthly) assessments and escalation of treatment (step-up therapy), which again might ultimately involve combination DMARD therapy alongside local and systemic glucocorticoids. Joint damage, long-term functional disability, and mortality have all been shown to benefit from such targeted approaches to disease activity. Many professional societies and regulatory agencies, including EULAR, ACR, and NICE publish and regularly update guidelines for rheumatoid arthritis management. In the United Kingdom, NICE has also published quality standards which incorporate early treatment and treatment-to-target. Early and aggressive intervention means that up to half of rheumatoid arthritis patients can now achieve disease remission early in the disease course. Indeed, remission should be the target of disease control for most patients. In others the disease is more difficult to control, reflecting both undefined prognostic factors and, probably, treatment delay. Such patients may cycle through various conventional synthetic anti-rheumatic drugs, often in combination, and subsequently receive biological and targeted synthetic therapies. Nevertheless, even if remission proves unachievable, tight arthritis control to low activity levels affords better long-term outcomes compared to those patients with poorly controlled disease. Conventional synthetic disease-modifying anti-rheumatic drugs Although most conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) have been available for several decades, they remain the anchor of modern rheumatoid arthritis therapy (Table 19.5.12). When csDMARDs are used early, and in combination where necessary, they can be as effective as the newer targeted therapies. Nonetheless, most also have the potential to cause serious side effects including hepatitis and bone marrow suppression. These drugs tend to be slow-acting, taking several weeks or months to exert their full therapeutic effect. The modes of action for most csDMARDs remain unknown. Methotrexate Methotrexate is recommended as the first-choice DMARD by most if not all rheumatoid arthritis treatment guidelines (Fig. 19.5.16). It inhibits the enzyme dihydrofolate reductase, although how this translates into therapeutic efficacy is unknown. It is usually titrated upwards from a starting dose of 7.5–10 mg once weekly, according to tolerability and efficacy. Most patients require 15–25 mg per week for therapeutic benefit, which can take six to eight weeks to develop. Oral folic acid (at least 24 hours after methotrexate administration) is coprescribed to reduce the incidence of gastrointestinal side effects. Methotrexate is available in both oral and parenteral preparations; the latter route of delivery has greater bioavailability and causes fewer gastrointestinal side effects. It should not be coprescribed with other folate antagonists such as trimethoprim, to minimize the

serious adverse effect of bone marrow suppression. Intravenous folinic acid is the antidote to methotrexate and can be life-saving in cases of acute toxicity. Methotrexate is potentially teratogenic, and women of reproductive age must ensure they use adequate contraception during and for 6 months after receiving the drug. The development of breathlessness or cough in a patient taking methotrexate should raise the suspicion of pneumonitis, a rare idiosyncratic reaction which can occur at any time during therapy. A baseline chest radiograph and pulmonary function tests (PFTs) are recommended, and some rheumatologists recommend repeat PFTs at regular intervals during therapy. Methotrexate is also associated with hepatitis and, rarely, cirrhosis, and should be avoided in patients with pre-existing liver disease or those who drink alcohol to excess. It is renally excreted and should be avoided or used with extreme caution in patients with renal failure. All patients receiving methotrexate should receive regular monitoring of full blood count (FBC) and liver function tests (LFTs) as an early signal of impending toxicity.

19.5 Rheumatoid arthritis 4435 Sulfasalazine Sulfasalazine is a conjugate of 5-aminosalicylate with sulfapyridine and a common first-choice csDMARD in those patients for whom methotrexate is contraindicated: it can also be used in combination with methotrexate. Most patients receive 2–3 g daily in two divided doses which, like methotrexate, can take several weeks to work. Sulfasalazine is considered safe in pregnancy although does have a reversible adverse effect upon spermatogenesis. Side effects tend to occur in the first few months of therapy and close monitoring of FBC (neutropenia) and LFTs in this period is required. Orange discolouration of urine and tears is a frequent though harmless side effect of the medication, and headaches can occasionally be troublesome. Sulfasalazine can rarely provoke skin reactions and even a drug-induced lupus syndrome. The mode of action of sulfasalazine is poorly understood. Antimalarials

Hydroxychloroquine is used as a csDMARD in the treatment of rheumatoid arthritis although has only modest efficacy compared to methotrexate and sulfasalazine, and is similarly slow-acting. It lacks significant toxicity, however, and regular blood monitoring is not required. Rare hypersensitivity reactions, including Stevens–Johnson syndrome, can nonetheless occur. Hydroxychloroquine is often coprescribed with methotrexate, or as triple therapy with sulfasalazine. There is a small risk of visual disturbance via drug deposition in the cornea (reversible) or retina (irreversible), but the risk is much greater with chloroquine, which is rarely prescribed for rheumatoid arthritis in the United Kingdom or United States. Nonetheless, all patients taking hydroxychloroquine should have a baseline visual assessment and annual ophthalmological review thereafter. Hydroxychloroquine is generally considered safe in pregnancy although there are isolated reports of fetal ototoxicity with doses above 200 mg daily.

Leflunomide Leflunomide is an inhibitor of pyrimidine synthesis and was introduced as a csDMARD in the late 1990s. Its efficacy and side effect profile are similar to that of methotrexate, although with a lower risk of pneumonitis. It can also cause hypertension and hence blood pressure monitoring is required during therapy, particularly in the initial weeks. Leflunomide is teratogenic and should be avoided in women and men of reproductive age. The drug undergoes entero-hepatic recirculation and hence can persist in the body for up to two years after cessation. Where rapid reversal is required, washout with oral cholestyramine or activated charcoal is required.

Table 19.5.12 Commonly used conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy in rheumatoid arthritis. For full information please refer to the current prescribing information provided by the manufacturer

Drug	Dose	Cautions	Notable side effects	Monitoring requirements
Methotrexate	Oral, intramuscular or subcutaneous 15–25 mg once weekly	Contraindicated in pregnancy and breastfeeding, pre-existing liver		

disease, and bone marrow suppression. Should be used with caution in renal impairment and with pre-existing lung disease. Nausea, fatigue, bone marrow suppression, hepatotoxicity, pneumonitis Routine FBC, LFTs and U&Es for duration of therapy Baseline CXR and PFTs Sulfasalazine Oral 1–1.5 g twice daily Allergy to salicylates or sulphonamides, G6PD deficiency, impaired renal or hepatic function, bone marrow suppression, pregnancy Nausea, bone marrow suppression, hepatotoxicity, yellow/orange discolouration of urine and tears Routine FBC and LFTs at least for first year of therapy Hydroxychloroquine Oral 200 mg once to twice daily (should not exceed 6.5 mg/kg/day) Pre-existing maculopathy, renal impairment, liver impairment, psoriasis (can worsen), epilepsy (reduced seizure threshold) Nausea, vomiting, skin eruption including Steven-Johnson syndrome, maculopathy Baseline and annual ophthalmological examination for duration of therapy Leflunomide Oral 10–20 mg once daily Contraindicated in pregnancy and breastfeeding, renal impairment, liver impairment, severe hypoproteinaemia, bone marrow suppression Nausea, diarrhoea, hepatotoxicity, bone marrow suppression, hypertension, weight loss, pneumonitis (rare) Routine FBC, LFTs, blood pressure and weight for duration of therapy CXR, chest X-ray; FBC, full blood count; G6PD, glucose-6-phosphate dehydrogenase; LFTs, liver function tests; PFTs, pulmonary function tests; U&Es, urea and electrolytes. a Methotrexate should be coprescribed with oral folic acid, at a minimal dose of 5 mg once weekly to be taken at least 24 hours after the dose of methotrexate. b Methotrexate is only ever given once weekly in the treatment of rheumatoid arthritis. Greater sensitivity to methotrexate is seen in Japanese populations where doses prescribed usually do not exceed 10 mg per week. c Sulfasalazine may be prescribed in pregnancy where the benefits are felt to outweigh the risks—the daily dose should not exceed 2 g/day and folic acid supplement should be prescribed. Sulfasalazine is generally considered safe in breastfeeding. d A loading dose of leflunomide 100 mg once daily for three days may be given when starting the drug, though this can cause gastrointestinal upset and is often omitted in clinical practice. Based upon recommendations within the 2017 British Society of Rheumatology/British Health Professionals in Rheumatology guideline for the prescription and monitoring of non- biologic DMARDs (Ledingham et al. (2017). *Rheumatology*; 56(6):865–8), and the Summary of Product Characteristics of the individual drugs.

section 19 Rheumatological disorders 4436 Fig. 19.5.16 Algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on rheumatoid arthritis (RA) management. ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; bDMARD, biological DMARD; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; MTX, methotrexate; RF, rheumatoid factor; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs. Reproduced from *Annals of the Rheumatic Diseases*, Smolen et al, volume 76, pages 960–77, copyright 2017 with permission from BMJ Publishing Group Ltd.

19.5 Rheumatoid arthritis 4437 Other csDMARDs Parenteral gold was a popular csDMARD in the 1970s and 80s, though is now infrequently used due to its side effect profile. Its use in modern practice tends to be reserved for patients in whom alternative DMARD therapy is either ineffective or contraindicated. Other older csDMARDs such as D-penicillamine, ciclosporin, and azathioprine are now very rarely used in the treatment of rheumatoid arthritis. Biological DMARDs Advances in understanding of the molecular pathogenesis of rheumatoid arthritis coupled with developments in pharmaceutical bioengineering have led to an explosion of biological DMARDs (bDMARDs) over

the past two decades. These are highly specific therapies, characterized by potent and selective targeting of a single molecule. Owing to their protein structure, bDMARDs are administered parenterally. Commonly used bDMARDs in rheumatoid arthritis are listed in Table 19.5.13. In brief, there are four classes of bDMARD currently licensed for rheumatoid arthritis treatment, which neutralize TNF, deplete B cells, prevent T-cell costimulation by APCs, or block IL-6 signalling. When bDMARDs were first introduced there was significant concern regarding the potential for long-term side effects. These concerns have abated somewhat with increasingly reassuring data from biologic registries. Nonetheless, compared with csDMARDs, their use is associated with an approximately 20% increased risk of serious infection, which is similar across the drug classes. The risk is not uniform across all patients, however, and factors such as previous severe infection, current glucocorticoid use, chronic lung or renal disease, and age each impact upon infection risk. Specific infections are increased with the use of particular therapeutic classes, most notably mycobacterial infections and anti-TNF therapy; patients should be screened for latent tuberculosis and, if positive, receive prophylactic anti-tuberculous therapy before commencing treatment. Compared to csDMARDs there does not appear to be an enhanced risk of solid organ malignancy, nonmelanoma skin cancer or lymphoma with bDMARD use, although the risk of malignant melanoma is increased for anti-TNF therapy, particularly in patients with a previous history of this malignancy. Nonetheless, caution is still recommended in the use of bDMARDs in patients with a prior history of malignancy. bDMARDs are expensive agents and have been the subject of intense health economic scrutiny. In the United Kingdom, guidelines on their use have been introduced by NICE, restricting their prescription to patients with highly active disease that is resistant to at least two csDMARD therapies and requiring documentation of improved disease activity with treatment. As with csDMARDs, there is response heterogeneity for bDMARDs among rheumatoid arthritis patients—good responses to one therapy are not predictive of similarly good responses to another. No biomarkers have yet been identified that predict bDMARD efficacy, with the sequence of bDMARD use dictated largely by financial cost and clinician experience. The recent introduction of biosimilar bDMARDs should significantly reduce the cost of therapy and could potentially change the future availability of these treatments.

Targeted synthetic DMARDs Targeted synthetic DMARDs (tsDMARDs) comprise a new category of orally bioavailable drugs for rheumatoid arthritis. Janus kinase inhibitors (JAKi) comprise the first class of tsDMARDs. JAKs are a family of four membrane-associated protein tyrosine kinases that are required for the signalling of several cytokines and haematopoietic growth factors. The selectivity of the JAKi, and hence their potential therapeutic profile, varies. Tofacitinib is most selective for JAK 3 and JAK 1, baricitinib for JAK 1 and JAK 2. JAKi with different selectivities are in development. Tofacitinib and baricitinib have a rapid onset of action and can be prescribed as monotherapy or in combination with other csDMARDs for patients with rheumatoid arthritis who do not respond to or are intolerant of methotrexate. As with bDMARDs, their use is subject to guidelines from bodies such as NICE. To date, the adverse event profile of JAKi appears similar to bDMARDs with the exception of a higher incidence of herpes zoster reactivation. JAKi must not be prescribed in combination with biological DMARDs or potent immunosuppressants such as azathioprine and cyclophosphamide.

Glucocorticoids Glucocorticoids are highly potent anti-inflammatory drugs, which can deliver a rapid and profound suppression of synovitis. When first introduced in the 1950s, they were seen as a miraculous ‘cure’ for rheumatoid arthritis; unfortunately, the now familiar spectrum of serious long-term side effects limits their use as maintenance therapy. Nonetheless, glucocorticoids still play an important role in rheumatoid arthritis management, particularly in the initial stages of disease, or when switching therapy, as a ‘bridging measure’ to control inflammation while waiting for DMARDs to act. Similarly, they

provide rapid symptomatic relief during an arthritis flare. When using glucocorticoids in rheumatoid arthritis, the central aim is to use as low a dose as possible for the shortest possible duration. Tapering courses of oral prednisolone can be used, or alternatively deep intramuscular depot injections such as depomedrone Table 19.5.13 The mechanism of action of biological DMARDs commonly used in the treatment of rheumatoid arthritis (see Chapter 2.7 for further details)

Biologic agent Nature Mechanism of action

Infliximab Chimeric human/mouse anti-TNF α antibody Bind to and neutralise TNF α

Etanercept Fusion protein of extracellular domain of p75 TNF α receptor with human IgG1 Fc

Adalimumab Human IgG1 anti-TNF α antibody Certolizumab pegol PEGylated humanized anti-TNF α Fab' fragment

Golimumab Human IgG1 anti-TNF α antibody Sarilumab Human IgG1 anti-IL6 receptor antibody Prevent IL6 binding to its receptor

Tocilizumab Humanized anti-IL6 receptor antibody Abatacept Fusion protein of extracellular domain of CTLA-4 with human IgG1 Fc Blocks costimulation of T cells via CD28

Rituximab Chimeric human/mouse anti-CD20 antibody Depletes CD20 positive B cells

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; Ig, immunoglobulin; IL, interleukin; TNF α , tumour necrosis factor alpha.

section 19 Rheumatological disorders 4438 (80–120 mg) or triamcinolone acetonide (40–80 mg). Single or multiple joints can also be injected with glucocorticoid to provide symptomatic relief while minimizing systemic adverse effects, and this is the preferred route when just a few joints are inflamed. With repeated or prolonged courses of glucocorticoid therapy come increasing risks of adverse effects. Gastro-protection with a proton-pump inhibitor or H₂-receptor antagonist should be offered under these circumstances. Prophylaxis against the development of osteoporosis, such as vitamin D replacement, calcium supplements, and anti-resorptive therapies should also be provided. Periodic screening for the development of steroid-induced diabetes mellitus is recommended, as is tight control of other cardiovascular risk factors. Finally, it is important to remember that glucocorticoids carry a dose-related infection risk, the highest of all rheumatoid arthritis therapies. Enhanced vigilance is thus required, especially because glucocorticoids can mask the typical clinical and laboratory features of sepsis. Nonsteroidal anti-inflammatory drugs NSAIDs play a useful role in the relief of the pain and stiffness of rheumatoid arthritis and, until recently, were prescribed chronically to many patients. However, they do not prevent joint damage, and the recognition that they predispose to cardiovascular disease in addition to their long-recognized renal and gastric toxicity now limits their long-term use. When NSAIDs are used, it is preferable to prescribe agents with lower cardiovascular risk such as naproxen and ibuprofen. Specific cyclooxygenase-2 (COX-2) inhibitors afford reduced gastric toxicity, although concerns regarding their cardiovascular toxicity profile have limited their more widespread use in clinical practice. Nonpharmacological management Nonpharmacological management is crucial for the effective and holistic treatment of rheumatoid arthritis. Basic medical care should not be overlooked such as blood pressure and cholesterol control, smoking cessation and immunization with appropriate (nonlive) vaccines such as influenza and pneumococcus. Patient education via leaflets, websites, and support groups are important to help patients understand the nature of their disease, the importance of effective treatment and to offer guidance on the practicalities of living with a chronic illness such as rheumatoid arthritis. Although the rheumatologist plays a central role in the provision of care, the support of and cooperation with other health professionals within a multidisciplinary team is paramount to successful rheumatoid arthritis management (Table 19.5.14). Rheumatoid arthritis is now viewed as a partnership between the patient and the

multidisciplinary team, with the best outcomes arising when an empowered patient enters an effective partnership with a broadly skilled team. With less joint damage as a result of improved medical management, there is now a reduced role for surgery in the treatment of rheumatoid arthritis. Nevertheless surgical intervention in the form of nerve decompression, synovectomy for refractory synovitis, and tendon reconstruction is sometimes required. Joint replacements are also occasionally required to improve pain and function of damaged joints but a partnership is equally important here, such that the patient understands the likely results of surgery. Prognosis

Many clinical factors have been associated with increased radiographic progression and poor functional outcomes in observational cohort studies of rheumatoid arthritis (Table 19.5.15). Not all factors have been replicated in all studies, and their independence from each other is debatable. Arguably the greatest

Table 19.5.14 The multidisciplinary team management of rheumatoid arthritis

Professional Team role	Management of rheumatoid arthritis
Rheumatologist	Diagnoses rheumatoid arthritis, monitors disease activity, prescribes DMARDs, monitors for complications of disease and therapy
Rheumatology specialist nurse	Supports role of rheumatologist, provides patient support and education, acts as coordinator of care
General practitioner	Makes initial referral to rheumatologist, assists with DMARD prescription and monitoring, vaccination, assists with cardiovascular risk modification
Orthopaedic surgeon	Synovectomy, joint fusion, nerve decompression, spinal fixation, joint replacement
Pharmacist	Dispensing DMARDs, may assist with DMARD monitoring
Physiotherapist	Exercise and joint strengthening
Occupational therapist	Joint protection (behavioural, splints and education), modifications to home and work environments
Podiatrist	Fits orthotic devices and provides foot care
Social worker	Advises on employment opportunities, coordinates welfare benefits and home care arrangements
Psychologist	Counselling, cognitive behavioural therapy (e.g. for depression and fatigue)

Table 19.5.15 Poor prognostic factors for increased joint damage in rheumatoid arthritis. Note that not all factors have been replicated in all studies, and the independence of each factor is debatable

- Older age at onset
- Female gender
- Longer duration of disease at diagnosis
- Delay in treatment initiation
- Erosions at presentation
- Raised BMI
- Cigarette smoking
- Socioeconomic deprivation
- Low educational attainment
- Extra-articular features
- Anaemia of chronic disease
- High cumulative levels of inflammation (clinical and biochemical measures)
- Rheumatoid factor positive (particularly IgA subtype)
- ACPA positive
- Shared epitope positive
- Baseline serum matrix metalloproteinase-3 (MMP-3) level
- Bone oedema on MRI
- Bone mineral density loss in first year measured by bone densitometry
- Power Doppler synovitis on ultrasound (in some studies)

Adapted from Markatseli et al 2010 Clin Exp Rheumatol; 28: 114-123.

19.5 Rheumatoid arthritis

4439 single factor governing long-term prognosis in rheumatoid arthritis is the adequacy of disease control at an early stage. Long duration of symptoms at diagnosis, delay in initiation of DMARD therapy and high disease activity in the first year after diagnosis are all strongly associated with poor long-term outcomes, including joint damage, disability, cardiovascular comorbidity, and increased mortality. Some investigations carry prognostic value, most notably seropositivity for RF and especially ACPA, which are both associated with more aggressive arthritis and increased incidence of erosive disease and extra-articular manifestations. A persistently elevated acute-phase response also portends a poor outcome. Musculoskeletal imaging may also have a role in prognostication, with some studies suggesting that patients in clinical remission but with active power Doppler synovitis on ultrasound scans are more likely to experience future arthritis flares and joint erosions compared to patients without this finding. Nevertheless, recent trials exploring the escalation of therapy to achieve ultrasound-defined

targets of disease control have failed to show superiority when compared to clinical disease activity targets alone. Complications of rheumatoid arthritis

Accelerated atherosclerosis

The cardiovascular (CV) complications of rheumatoid arthritis make the largest contribution to excess mortality. Accelerated atherosclerosis is a key comorbidity of rheumatoid arthritis, and is secondary to the effects of chronic inflammation and medications (e.g. glucocorticoids and NSAIDs) in addition to traditional CV risk factors such as reduced physical activity. Whereas CV mortality has fallen sharply over past decades in the general population, there has been very little change in rheumatoid arthritis, suggesting that control of traditional CV risk factors alone is not sufficient. However, recent epidemiological evidence suggests a reduction of CV risk with improved disease control, although these observations remain to be confirmed in long-term prospective trials.

Pulmonary Lung disease

Lung disease is common in rheumatoid arthritis and while some manifestations are clearly extra-articular features of active disease others, such as bronchiectasis, are becoming incriminated in disease aetiology albeit via uncertain mechanisms. Because smoking is a risk factor for rheumatoid arthritis, conditions such as chronic obstructive pulmonary disease and bronchogenic carcinoma are more common in rheumatoid arthritis populations. Furthermore, pneumonitis is an idiosyncratic adverse effect of several DMARDs, including methotrexate and leflunomide.

Infection

Patients with rheumatoid arthritis are at increased risk of infection, both as a consequence of the immune dysregulation underlying the disease and the immunosuppressive drugs used to control it. Discriminating infection from the acute-phase response and low grade pyrexia associated with widespread synovitis can sometimes pose a clinical challenge.

Renal

Renal manifestations that are directly attributable to rheumatoid arthritis are uncommon and largely confined to isolated cases of systemic amyloidosis and glomerulonephritis. Nevertheless, renal complications are frequently observed in patients with rheumatoid arthritis secondary to nephrotoxic drug use, especially NSAIDs, and were historically seen with older csDMARDs such as gold and D-penicillamine.

Other autoimmune diseases

The systemic autoimmunity at the heart of rheumatoid arthritis pathogenesis leads to an increased risk of other autoimmune diseases for which the clinician needs to be vigilant. For example, the incidence of autoimmune hypothyroidism is increased in rheumatoid arthritis, though can be mistakenly overlooked given the chronic fatigue experienced by patients with active arthritis. Type I diabetes mellitus is also more frequently encountered in the rheumatoid arthritis population, the control of which may be destabilized by glucocorticoid therapy.

Future developments

Stratified medicine

It is apparent that rheumatoid arthritis is a heterogeneous condition, with multiple distinct immunopathological pathways leading to a common clinical phenotype. Nevertheless, current rheumatoid arthritis therapy adopts a 'one size fits all' approach, with limited scope for individualization of treatment, and appropriate biomarkers are urgently required to underpin personalized management of rheumatoid arthritis (Fig. 19.5.17). For example, robust prognostic biomarkers would allow the early targeting of aggressive therapy to those patients most likely to develop future disability. Furthermore, biomarkers that predict response to drug therapy would enable intelligent selection of DMARDs most likely to benefit individual patients. Additional biomarkers could even help guide the tapering of DMARD therapy in patients who have achieved remission. Recent advances in high-throughput analytic techniques, collectively referred to as the 'omics' technologies (e.g. transcriptomics, proteomics, metabolomics), offer the potential to search for biomarkers within literally hundreds of thousands of biological parameters. However, considerable challenges remain in the assimilation of the vast datasets generated and the translation of these findings into diagnostic assays that are appropriate for routine clinical use. It is possible that such biomarkers will be found in the synovium rather than in the blood, catalysing a significant change in practice. In

oncology, for example, tissue biomarkers increasingly guide treatment choices. When these challenges are Disease flare Early diagnosis Prognosis Predictive RA biomarkers DMARD response DMARD-free remission Fig. 19.5.17 The categories of potential predictive biomarkers that would be of clinical value in the management of rheumatoid arthritis.

section 19 Rheumatological disorders 4440 overcome, stratified medicine will not only improve long-term outcomes but also reduce the cost of therapy. Preventative medicine Given the prodromal period of immune dysregulation that precedes the clinical onset of rheumatoid arthritis, recent interest has focused on whether rheumatoid arthritis could be prevented by targeting pre-rheumatoid arthritis. It should be easier to correct dysfunctional pathways of autoimmunity before they become fully established, possibly requiring only short periods of relatively mild therapy. Nonetheless, the potential benefits of such prophylactic interventions would need to be carefully balanced against the potential side effects, while considering the ultimate risk of developing rheumatoid arthritis. However, even lifestyle modification measures such as attending to dietary factors and smoking cessation, could be effective in preventing rheumatoid arthritis in at-risk individuals. Microbiome modification could also halt progression to clinical disease. New therapeutic targets Despite recent therapeutic advances, a proportion of patients with rheumatoid arthritis remain resistant to currently available therapies and consequently there remains a demand for new therapies with diverse modes of action. Current therapies target the known immunopathology of rheumatoid arthritis, with little attention directed towards the joint stroma. Given recent observations that FLS play an important role in the pathogenesis of rheumatoid arthritis, they provide an attractive target for future therapeutic approaches. These include anti-proliferative drugs, pro-apoptotic drugs, or even epigenetic modifiers; potential compounds already exist in the oncology armamentarium. Therapeutic tolerance The ultimate therapy for rheumatoid arthritis would be an immune manipulation that abrogates autoimmunity and restores self-tolerance, removing the need for long-term immunosuppression. Therapeutic tolerance to organ allografts and experimentally-induced autoimmunity is achievable in animal models. It has also recently been demonstrated through haematopoietic chimerism in human renal transplant recipients. In addition to targeting of the immune system in vivo, tolerogenic conditioning of autologous or heterologous immune cells ex vivo and their use as a cellular therapy is another route to potentially achieving therapeutic tolerance. If effective, such tolerogenic therapies would revolutionise the treatment of rheumatoid arthritis by providing sustained benefit from a single short course of therapy, probably delivered at an early stage of the disease. FURTHER READING Aletaha D, et al. (2010). Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*, 69, 1580–8. Bottini N, Firestein GS (2013). Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors. *Nat Rev Rheumatol*, 9, 24–33. Bottini N, Firestein GS (2013). Epigenetics in rheumatoid arthritis: a primer for rheumatologists. *Curr Rheumatol Rep*, 15, 372. Ledingham, et al. (2017). BSR and BHPR guideline for the prescription and monitoring of nonbiologic disease-modifying anti-rheumatic drugs. *Rheumatology*, 56, 865–8. Choudhary MM, Hajj-Ali RA, Lowder CY (2014). Gender and ocular manifestations of connective tissue diseases and systemic vasculitides. *J Ophthalmol*, 2014, 403042. Cross M, et al. (2014). The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*, 73, 1316–22. Doran MF, et al. (2002). Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis Rheum*, 46, 625–31. England BR, et al. (2016). Cause-specific mortality in male US veterans with rheumatoid arthritis. *Arthritis Care Res*, 68, 36–45. Felson DT, et al. (2011). American College of Rheumatology/European League against

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