

Rheumatoid arthritis

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Abstract | Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease that primarily affects the joints and is associated with autoantibodies that target various molecules including modified self-epitopes. The identification of novel autoantibodies has improved diagnostic accuracy, and newly developed classification criteria facilitate the recognition and study of the disease early in its course. New clinical assessment tools are able to better characterize disease activity states, which are correlated with progression of damage and disability, and permit improved follow-up. In addition, better understanding of the pathogenesis of RA through recognition of key cells and cytokines has led to the development of targeted disease-modifying antirheumatic drugs. Altogether, the improved understanding of the pathogenetic processes involved, rational use of established drugs and development of new drugs and reliable assessment tools have drastically altered the lives of individuals with RA over the past 2 decades. Current strategies strive for early referral, early diagnosis and early start of effective therapy aimed at remission or, at the least, low disease activity, with rapid adaptation of treatment if this target is not reached. This treat-to-target approach prevents progression of joint damage and optimizes physical functioning, work and social participation.

In this Primer, we discuss the epidemiology, pathophysiology, diagnosis and management of RA.

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease of autoimmune nature characterized by autoantibodies to immunoglobulin G (IgG; that is, rheumatoid factor (RF)) and citrullinated proteins (that is, anti-citrullinated protein antibodies (ACPAs)). If insufficiently treated, RA can lead to accumulating joint damage and irreversible disability. RA is a heterogeneous disease, with variable clinical presentation and pathogenetic mechanisms involved between individuals with the same formal diagnosis or across different disease stages. Indeed, although autoantibodies are an important characteristic of RA (seropositive RA), some individuals are negative for these autoantibodies (seronegative RA). The disease is complex and involves environmental factors that trigger disease in genetically susceptible individuals¹ (FIG. 1).

Over the past 2 decades, we have witnessed new genetic and pathogenetic insights and an update of classification criteria that comprise information from cohorts of patients with very early RA as well as newly characterized autoantibodies to facilitate early recognition of the disease. New developments in disease assessment and therapeutic strategies, and the evolution and approval of a variety of novel therapies, have also been reported. Altogether, the tremendous evolution of the field has considerably improved the prognoses of most

individuals with RA. Although we can not yet cure RA, remission is now an achievable goal. However, many patients still cannot attain remission and more work is needed to provide every patient with the benefit of therapeutic success.

This Primer on RA provides the latest insights into the epidemiology, genetics, pathophysiology, diagnostic approaches, clinical assessment and management of RA. In addition, this Primer examines as-yet unmet needs and provides an outlook on how to tackle the outstanding issues to attain an even brighter future for all individuals with RA.

Epidemiology

Global prevalence

Although the prevalence of RA in some regions is not known owing to the lack of robust epidemiological studies, the reported rates seem fairly constant in many populations². Most epidemiological studies in RA have been done in Western countries, showing a prevalence of RA in the range of 0.5–1.0% in white individuals^{2,3}. Although robust epidemiological studies are limited in other areas, the few data we have point towards a similar range. For example, the prevalence of RA in Kinshasa, Democratic Republic of the Congo, is 0.6% in the general black population and 0.9% in black individuals aged >18 years,

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which seems to be similar to the numbers reported in Western countries⁴. However, the prevalence of RA differs between ethnicities. A high prevalence of 5–6% has been reported in Native American populations⁵. The adjusted prevalence ratios were 0.45, 0.69 and 1.02 for women of Hispanic, Asian or African-American descent, respectively, compared with white women, as presented in a meeting abstract⁶. Finally, geographical differences have been reported, although studies are limited. For example, a lower prevalence has been reported in southern Europe than in northern Europe³.

Risk factors

Several risk factors are known to be involved in the development of RA, including genetics, female sex and environmental factors. Proposed environmental risk factors include smoking, silica exposure, infectious agents, vitamin D deficiency, obesity and changes in the microbiota (FIG. 1), although studies for some of these factors are not very robust.

Genetics. RA has a strong genetic component. For example, twin studies have estimated that the heritability (the proportion of phenotypic variance that is due to genetic variance in a population) of RA is ~60%⁷. This pertains to RA patients who are positive for ACPAs⁸, whereas estimates in seronegative disease are lower⁹. However, identical twins show a disease concordance of only 12–15%, which indicates that non-coding factors play an important role in susceptibility.

Specific class II human leukocyte antigen (*HLA*; also known as major histocompatibility complex (MHC)) loci, which encode MHC molecules that may contain the shared epitope, show a very strong association with RA¹⁰. The shared epitope is a specific amino acid motif commonly encoded by some alleles of the HLA-antigen D related (DR) locus, especially *HLA-DRB1*01* and *HLA-DRB1*04*, which are significantly associated with the risk of developing RA¹⁰. However, other risk loci with weaker associations have also been identified, the majority of which are associated with immune and inflammatory pathways^{11,12}. Genome-wide association studies^{13–15} with fine mapping¹⁶, candidate gene approaches^{10,17–20} and a meta-analysis¹² of genome-wide association studies involving >100,000 individuals,

combined with, among others, functional annotation and pathway analysis, have identified ~100 loci across the genome harbouring RA susceptibility variants. Many of the proteins encoded by these genes can potentially be targeted by therapeutic agents¹². Although many alleles associate only weakly with RA and likely interact with other genes and the environment²¹, modest cumulative effects have been observed when several risk alleles are present²². Additionally, genetic differences between ACPA-positive and ACPA-negative RA have been revealed²³. For example, variants in *HLA-DRB1*, *PTPN22*, *BLK*, *ANKRD55* and *IL6ST* associate with RA regardless of serological status whereas *AFF3*, *CD28* and *TNFAIP3* are found only in seropositive RA and *PRL* and *NFIA* are found only in seronegative RA^{23,24}.

The variants associated with RA commonly map to enhancer regions²⁵, which can regulate one or more genes at distant locations in a cell-type-specific manner. Thus, genetic susceptibility variants mapping to apparently different regions of a chromosome may regulate the same gene^{26,27}. Understanding this complex regulation is vital to define which genes are important in which cell types for the predisposition to RA, which will, in turn, contribute to the identification of key pathways driving disease and enable stratification of the RA population into groups based on the causative pathway.

Thus far, most studies have focused on understanding susceptibility to RA but equally important are studies that aim to identify biomarkers of disease severity. Indeed, several RA susceptibility genes are also associated with severity (for example, *HLA-DRB1*, *IL2RA*, *DKK1*, *GRZB*, *MMP9* and *SPAG16*)^{28,29}. However, evidence is emerging to support the existence of genes that are associated with severity alone, including *FOXO3* (REFS 28,30). Similarly, predicting treatment success would be a major advance, but no genetic biomarkers have yet been robustly and consistently identified, partly because of the small sample sizes and limited power of the studies³¹.

Epigenetics. Studies have shown that genetic variants associated with RA are enriched in epigenetic marks of active chromatin in CD4⁺ T helper cells²⁵. Epigenetics, including DNA methylation and histone acetylation, might have a role in RA development. In monozygotic twin pairs discordant for RA, DNA methylation at *EXOSC1* (encoding a protein involved in RNA degradation) differed between the affected and the unaffected twin³². The largest DNA methylation study of RA in unrelated individuals identified nine clusters with a differential methylation pattern in the HLA region compared with healthy controls, suggesting that the genetic effect of HLA risk variants acts, in part, by virtue of altered DNA methylation³³. DNA methylation provides a mechanism through which environmental factors can induce changes in cellular activity. For example, in smokers, methylation levels were higher in individuals with ACPA-positive RA who carried the *HLA-DRB1* risk allele than in those who did not carry the risk allele; this difference in methylation was not observed in nonsmokers³⁴. Interestingly, two studies have reported that different patterns of DNA methylation and transcription occur in fibroblast-like

synoviocytes (FLS) from different joints in patients with RA; this finding may provide a mechanism to explain why RA tends to be symmetrical and affects some joints more severely than others³⁵.

Sex. In general, women are twofold to threefold more likely to develop RA than men³⁶. Indeed, the cumulative lifetime risk of developing adult-onset RA has been roughly estimated at 3.6% for women and 1.7% for men³⁷. The higher frequency of RA in women is attributed, in part, to the stimulatory effects of oestrogen on the immune system; however, the role of hormonal factors in the development of RA remains controversial³⁸. In women, nulliparity often increases the risk of RA, whereas pregnancy is often associated with disease remission, although disease flares are common in the post-partum period. In women, RA most commonly becomes symptomatic around middle age or at the time of menopause. Men have a later disease onset, are more likely to be positive for RF and have higher titres of ACPAs³⁹.

Smoking. Tobacco smoking raises the risk of RA in a graded fashion, with a doubling of the risk among current smokers with a 20-pack-year history of tobacco use compared with nonsmokers^{40,41}. The association between tobacco use and RA is strongest or even restricted to ACPA-positive disease in individuals with at least one copy of the shared epitope⁴². Indeed, the interaction between the

shared epitope and smoking can increase risk by 20-fold or more compared with nonsmokers who do not carry the shared epitope⁴². Current smoking status is associated with increased levels of pro-inflammatory cytokines and increased RA disease activity⁴³. The increased risk associated with smoking might be mediated by epigenetic modifications, as smoking was significantly associated with hypomethylation of certain DNA regions, whereas disease-modifying antirheumatic drug (DMARD) treatment induced hypermethylation of the same regions⁴⁴. Interestingly, the non-nicotine inhaled components of cigarette smoke are thought to increase the risk of RA whereas the tobacco component does not⁴⁵. However, the association between smoking and RA remains controversial as some studies report conflicting evidence^{41,46}.

Dust inhalation. Silica exposure is an environmental risk factor for RA⁴⁷. Indeed, a study of firefighters and other emergency responders exposed to dust at the site of the 2001 World Trade Center collapse in New York, United States, found an increased risk of systemic autoimmune diseases, including RA⁴⁸. The dust contained pulverized cement, silica, asbestos, glass fibres and other materials. Occupational exposure to textile dust was also found to be significantly associated with an increased risk of developing RA in a population of Malaysian women⁴⁹. The association was observed for both ACPA-positive RA and ACPA-negative RA.

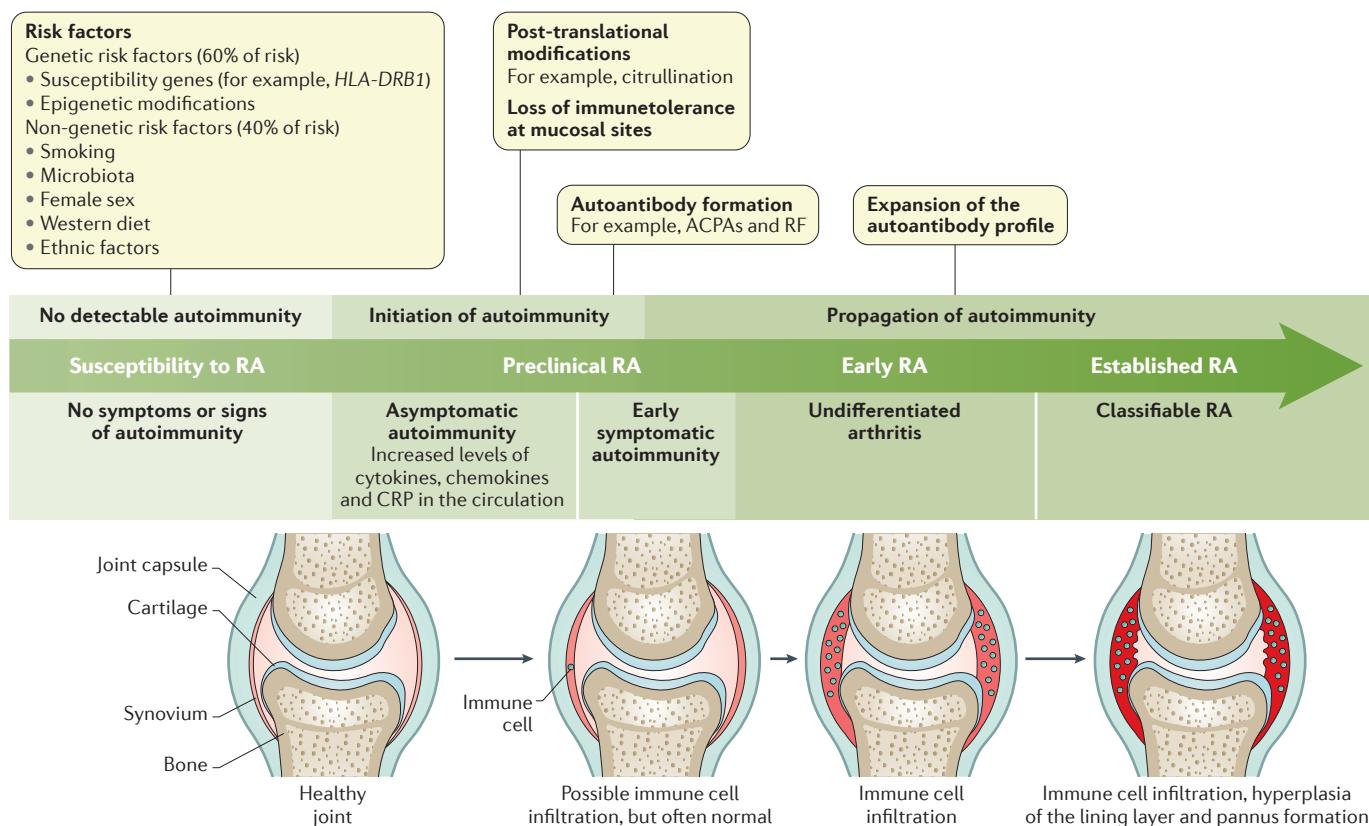


Figure 1 | Development and progression of RA. Both genetic and non-genetic risk factors contribute to rheumatoid arthritis (RA), and multiple risk factors are likely required before a threshold is reached above which RA is triggered. Disease progression involves initiation and

propagation of autoimmunity against modified self-proteins, which can occur years before the onset of subclinical synovitis (inflammation of the synovium) and clinical symptoms. ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; RF, rheumatoid factor.

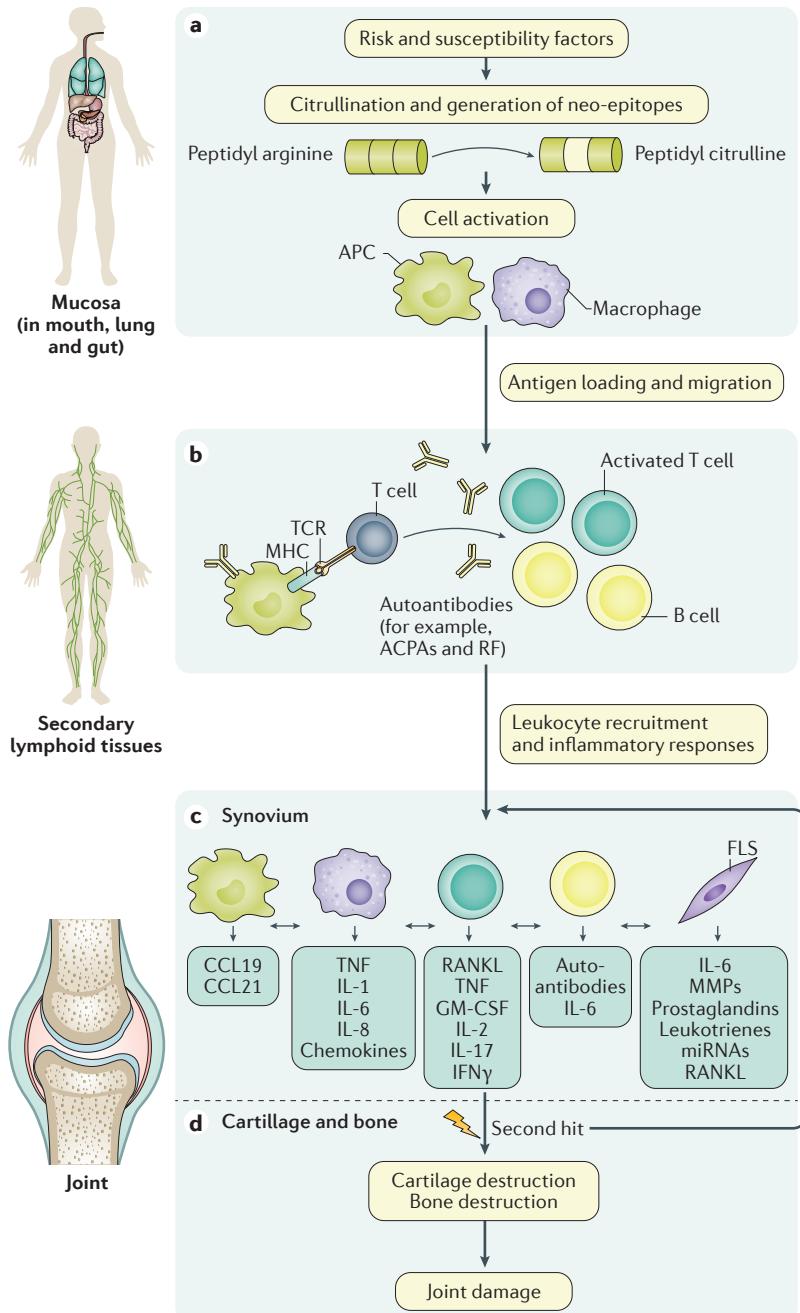


Figure 2 | Mechanisms involved in initiation and progression of rheumatoid arthritis.

a | Post-translational modifications, such as by citrullination or carbamylation, in the mucosa can create neo-epitopes that can be recognized by the adaptive immune system.

b | These altered peptides are presented by antigen-presenting cells (APCs), activate an adaptive immune response in lymphoid tissues and elicit autoantibody formation.

c | Stromal cells (such as fibroblast-like synoviocytes (FLS)), APCs and macrophages can be activated locally and produce a range of inflammatory factors. The autoimmune response elicited by the immune system triggers synovial inflammation but may require a second hit, such as immune complex formation and complement activation, to induce or increase cytokine production and synovial vascular leakage. **d** | Paracrine and autocrine actions of cytokines, along with persistent adaptive immune responses, can perpetuate the disease and ultimately lead to cartilage and bone destruction. APCAs, anti-citrullinated protein antibodies; CCL19, CC-chemokine ligand 19; CCL21, CC-chemokine ligand 21; GM-CSF, granulocyte-macrophage colony-stimulating factor; MHC, major histocompatibility complex; miRNA, microRNA; MMP, matrix metalloproteinase; RANKL, receptor activator of nuclear factor- κ B ligand; RF, rheumatoid factor; TCR, T cell receptor; TNF, tumour necrosis factor.

Microbiota. Periodontal disease is also associated with an increased risk of developing RA⁵⁰. Although periodontal disease and RA seem clinically very distinct, their pathogeneses bear similarities with chronic inflammation and inflammatory bone erosions. Interestingly, the association between RA and periodontal disease is thought to be partly mediated by the oral microbiota, for example, *Porphyromonas gingivalis*⁵¹ and *Aggregatibacter actinomycetemcomitans*⁵² (see below).

Aside from periodontal microbiota, the gut microbiota may play an important role in disease, and the diversity of gut microbiota is decreased in individuals with RA compared with the general population. Indeed, rare taxa, such as Actinobacteria, are expanded in individuals with RA, whereas the diversity of abundant taxa is reduced⁵³. Interestingly, intestinal levels of *Prevotella copri* seem to mark early disease, as this bacterium is more common in untreated patients with new-onset RA than in those with established RA or in those who do not have RA⁵⁴. In a recent study, peptides of two novel autoantigens with significant sequence homology with peptides of *Prevotella* and other gut bacteria species were isolated from HLA-DR molecules of patients with RA⁵⁵. This finding supports a link between environment, autoimmunity and disease. Regarding viruses, the role of parvovirus B19 infection in RA still remains to be fully elucidated⁵⁶, but Chikungunya virus infection, which usually leads to acute polyarthralgia (pain in several joints), can occasionally progress to RA-like pathologies⁵⁷. Interestingly, Epstein-Barr virus (EBV) infection has been associated with RA and other autoimmune disorders for many decades⁵⁸.

Others. Modifiable lifestyle factors have also been implicated in RA. For example, obesity has been consistently and independently associated with a modest increase in the risk of subsequent RA, with an odds ratio of 1.45 in those with a body mass index (BMI) of ≥ 30 kg per m² compared with those with a BMI of < 25 kg per m² (REF. 59). A modest association was found between long-term moderate alcohol consumption and reduced risk of RA⁶⁰. Women with high symptomatology of post-traumatic stress disorder also have an increased risk of developing RA⁶¹. Low socioeconomic status, including low educational level, has been found to be associated with worse outcomes of RA, although the studies supporting this possibility require further expansion⁶².

Mortality

Cardiovascular disease is the most common cause of premature death in individuals with RA. Patients with RA have high prevalence rates of cardiovascular risk factors; rates of hypertension, diabetes mellitus, hyperlipidaemia and obesity have been reported to be 18.6%, 6.0%, 9.9% and 4.4%, respectively⁶³. Serological and genetic factors can have a role in identifying individuals with RA who are at increased risk of cardiovascular disease⁶⁴. A prospective analysis of the Nurses' Health Study reported that women with RA had an increased risk of total mortality (HR = 1.40; 95% CI 1.25–1.57) compared with those without RA; respiratory disease

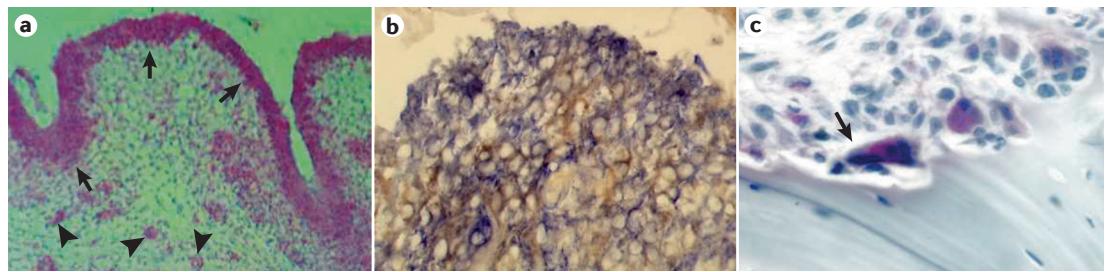


Figure 3 | Histological features of synovitis and joint destruction in RA. **a** | Synovitis associated with rheumatoid arthritis (RA) is characterized by hyperplasia of the lining layer (arrows), infiltration of immune cells in the sublining and hypervascularity (arrowheads). **b** | Many macrophage-like synoviocytes (blue staining based on CD68 staining) and fibroblast-like synoviocytes overexpress tumour necrosis factor (brown staining). **c** | Osteoclast (arrow) originating in the synovium invading the bone. Magnifications: panel **a** (50×), panel **b** (400×) and panel **c** (800×).

mortality ($HR = 2.06$; 95% CI 1.51–2.80) and cardiovascular disease mortality ($HR = 1.45$; 95% CI 1.14–1.83) were particularly increased, but cancer mortality was not ($HR = 0.93$; 95% CI 0.74–1.15). The risk of mortality due to respiratory diseases is increased by approximately threefold in women with seropositive RA compared with those without RA⁶⁵. However, with current treatment strategies, premature mortality is no longer observed⁶⁶.

Mechanisms/pathophysiology

Disease course

Preclinical RA. In most patients, the pathogenesis of RA begins years before clinical disease is evident, although acute onset reflecting immediate immune perturbation is also possible⁶⁷. Thus, RA is considered to be a continuum that begins with a high-risk or susceptibility stage that is primarily based on genetic factors, and proceeds through preclinical RA before articular inflammation (early RA) develops. Environmental factors operate across this continuum. Ultimately, established RA develops in those who have not self-resolved (FIG. 1). Discrete mechanisms are thought to operate across this pathological continuum, creating opportunities for stage-specific and individual-specific interventions that could abrogate or even prevent established disease.

RA development is determined by a predisposing genotype upon which environmental and genetic factors operate to ultimately result in the inflammatory and destructive synovial response (FIG. 2). How the environmental risk factors contribute to disease is incompletely understood. However, it seems that stressors in, for example, cigarette smoke can act on cells in mucosal sites and promote post-translational conversion of the amino acid arginine to citrulline in a range of proteins, including intracellular proteins (such as histones) and matrix proteins (for example, fibronectin, collagen, fibrinogen, enolase and vimentin) via induction of peptidyl arginine deiminases in a process called citrullination (also known as deimination)⁶⁸ (FIG. 2a). Citrullination may also be induced by the microbiota: *P. gingivalis*, which is common in periodontal disease, expresses peptidyl arginine deiminases and can induce citrullination and thereby promote ACPA generation⁶⁹. In addition, *A. actinomycetemcomitans*, which produces a toxin

that increases calcium influx into neutrophils, can lead to citrullination of peptides and has been recently implicated in RA aetiology⁵².

Following citrullination or other post-translational modifications (for example, acetylation or carbamylation), the altered peptides bind to MHC protein heterodimers, especially those containing the shared epitope, leading to antigen presentation to T cells, which in turn stimulate B cells to synthesize a range of antibodies that recognize self-proteins, including RF (targeting IgGs) and ACPAs (targeting citrullinated proteins)^{70,71} (FIG. 2b). Intriguingly, this process could be considered a normal immune response to an altered antigen rather than true autoimmunity. Other mechanisms of protein modification, such as acetylation or non-enzymatic carbamylation, are also likely to turn self-proteins into targets for autoantibody generation⁷².

The presence of circulating ACPAs, other antibodies (such as RF) and circulating pro-inflammatory cytokines and chemokines can be detected up to 10 years before clinical disease onset, which points to immune activation during the preclinical period. The presence of ACPAs, but also RF, is associated with a more aggressive disease course and can, therefore, be used not only as a diagnostic marker but also as a prognostic marker^{73–77}. ACPAs are heterogeneous, but their fine specificity (that is, the exact peptide recognition profile) does not seem to predict the clinical course^{78,79}. However, synovial biopsy samples of individuals positive for autoantibodies are often normal, even in the presence of arthralgia⁸⁰, although synovial infiltration with inflammatory cells may also be found in the absence of clinical signs and symptoms⁸¹. The presence of ACPAs alone is not sufficient to cause synovitis; an additional hit (for example, immune complex formation, complement activation or microvascular insult) is likely required to initiate clinical synovitis characterized by increased vascular permeability and influx of inflammatory cells into the synovium⁸² (FIG. 2c,d).

Early and established RA. Early RA is characterized by synovial inflammation based on mononuclear cell infiltration, dominated by CD4⁺ T cells and macrophages, together with early stromal cell activation (FIG. 2c). Synovial biopsy samples taken within 1 week of the onset

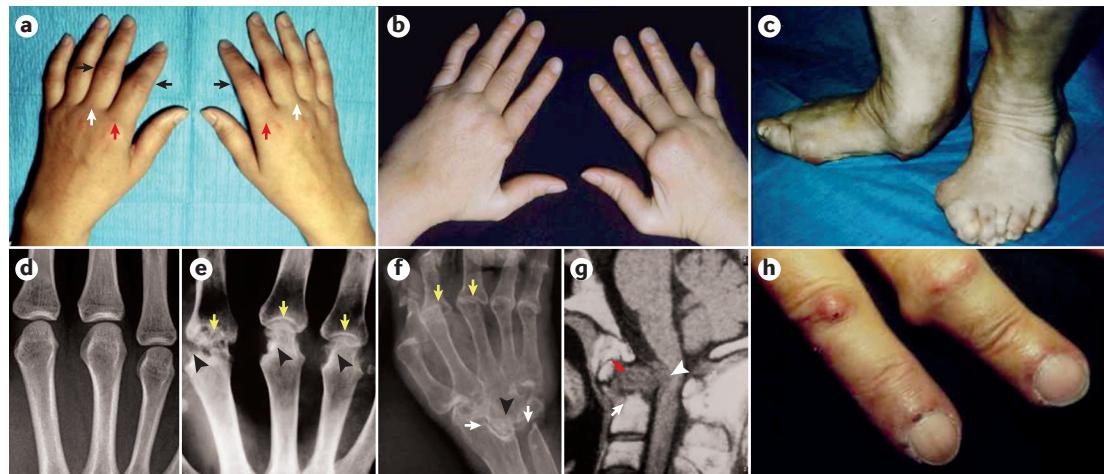


Figure 4 | Clinical manifestations of RA. Early rheumatoid arthritis (RA; part a), characterized by mild, hardly discernible swelling of the second (red arrow) and third (white arrow) metacarpophalangeal joints on both hands and several proximal interphalangeal joints (black arrows). Established RA (part b) with various deformities, including subluxation (that is, a partial or incomplete dislocation of the joint) at the metacarpophalangeal joints, swan-neck deformities of several fingers, most prominently seen at the fifth digit (the little finger), and a Z deformity of the thumb in the right hand. Late, severe RA (part c) with mutilating involvement of the ankle and foot joints. Hand radiographs ranging from normal (part d) to severe damage (parts e and f) with bone erosions (black arrow head, part e) and joint space narrowing that corresponds to loss of cartilage (yellow arrows, part e) and mutilating changes, where, for example, the joint space (cartilage) between the various small carpal bones is used up and they coalesce to almost form a type of a 'single' bone (that is, "os carpale"; black arrowhead, part f). Mutilating changes also involve pencil-in-cup deformities (yellow arrows, part f, point to the 'cup') and destruction of the distal radius and distal ulna where they interact with the carpus (white arrows, part f). MRI of the cervical spine (part g) shows severe pannus formation (red arrow) at the atlantodental joint with compression of the medulla (white arrowhead) due to synovial hyperplasia. The dens of the axis shows severe erosions (white arrow). Presence of rheumatoid nodules (part h) on the dorsal and lateral sides of several fingers and periungual vasculitis at the nailfolds (black dots). Parts d and e are adapted from REF. 248, Macmillan Publishers Limited.

of symptoms show high expression of matrix-degrading enzymes (such as matrix metalloproteinases (MMPs)) in the synovial intimal lining. In addition to ACPAs, other autoantibodies that recognize immunoglobulins (that is, RF), type 2 collagen (particularly in oxidized form), glucose-6-phosphate isomerase, proteoglycans, nuclear antigens and other joint autoantigens expand the pathways whereby autoantibodies likely contribute to pathogenesis⁸³.

Some interesting findings have emerged from comparing early disease with established disease. Most data suggest that pathogenetic pathways in the synovium are established early and remain remarkably stable over the ensuing years, although some differences have been reported; early RA is sometimes described as a 'window of opportunity' for these reasons⁸⁴. Typically, the ACPA profile expands before clinical disease onset, whereas the range of specificities does not further evolve with progression to established disease, consistent with an early pathogenetic role for these autoantibodies. Similar features over time have been described for RF and for other autoantibodies specific for, for example, anti-carbamylated peptides⁸⁵. However, upon effective treatment, levels of RF decrease more strongly than ACPA levels, suggesting a greater plasticity and/or different cellular origin of RF⁸⁶. In addition, expansion of plasmablasts, especially those that can produce isotype IgA ACPAs, is evident early in pathogenesis, consistent with a role for mucosal events in emerging disease⁸⁴.

T cells can sometimes exhibit clonality in early disease but become much more polyclonal, perhaps via dilution, as disease evolves, meaning that detection of disease-causing T cells in established disease is challenging⁸⁷. Finally, the role of macrophages and fibroblasts in perpetuating synovitis is more prominent in established disease. DNA methylation patterns in FLS isolated from individuals with early RA differ from those of individuals with established disease; pathway analysis showed that the main differences are found in cell differentiation, adhesion and proliferation⁸⁸.

Pathogenesis

The synovium. Although RA is a systemic disease and a variety of immunological events occur outside the joint at mucosal surfaces and primary lymphoid tissues (FIG. 2a,b), the synovium is a central player (FIG. 2c). The synovium serves two main roles in homeostasis: producing lubricants that enable the cartilage surfaces to operate in a low-friction environment and providing nutrients to cartilage, which lacks its own blood supply. A healthy synovium is a fairly delicate structure with an intimal lining composed of macrophage-like synoviocytes and FLS and a sublining composed of fibroblasts, adipocytes, blood vessels and scattered immune cells. The intimal lining is not a barrier in the traditional sense because it lacks a basement membrane and tight junctions, it is leaky and allows relatively free trafficking of cells and proteins into the synovial fluid⁸⁹.

Two key pathogenetic changes in the synovium are evident in RA (FIG. 3a,b). First, the intimal lining greatly expands owing to an increase and activation of both synoviocyte types⁹⁰, which are a prominent source of cytokines and proteases. The macrophage-like synoviocytes produce a variety of pro-inflammatory cytokines, including IL-1, IL-6, tumour necrosis factor (TNF) and others. Although FLS express IL-6, their most prominent feature is the production of prodigious amounts of MMPs and small-molecule mediators such as prostaglandins and leukotrienes⁹¹. FLS also express specific patterns of microRNAs that could contribute to their activated phenotype^{92,93}. In addition, FLS assume an invasive phenotype that is responsible for cartilage damage and can potentially migrate from joint to joint to propagate disease (discussed below)⁹⁴.

The second change associated with RA is infiltration of adaptive immune cells into the synovial sublining⁹⁵. About half of the sublining cells are CD4⁺ memory T cells that can either diffusely infiltrate the tissue or, in 15–20% of patients, form ectopic germinal centres in which mature B cells proliferate, differentiate and

produce antibodies. B cells, plasmablasts and plasma cells are also present, many of which produce RF or ACPAs. Studies of immunoglobulin gene rearrangements and the relevant tissue enzyme expression associated with ectopic germinal centres⁹⁶ suggest that autoantibody-producing cells (including those that produce IgG, IgM and IgA isotypes) undergo affinity maturation in the tissue, suggesting an ongoing immune response to native or altered peptides⁹⁷. However, the relative contribution of these synovial pathways to the overarching pathogenesis is unclear as the largest proportion of affinity maturation occurs before clinical disease onset⁹⁸. Antigen-presenting follicular dendritic cells, macrophages and mast cells are also distributed through the synovial sublining; neutrophils are curiously lacking. Some studies suggest that distinct subtypes of synovial histology (that is, pathotypes that include inflammatory versus non-inflammatory patterns) are associated with clinical phenotype or response to targeted agents⁹⁹.

Joint damage. Damage to cartilage and bone due to synovial invasion into adjacent articular structures is a cardinal sign of RA (FIG. 2d). The pathways involved in damage are likely heterogeneous and include distinct mechanisms between individuals who are ACPA positive and those who are ACPA negative and perhaps even those who have other autoantibodies. Macrophages, neutrophils (particularly in the synovial fluid space) and mast cells contribute to joint damage via release of cytokines and MMPs. However, the dominant destructive cell type for cartilage are considered the cadherin-11-positive FLS¹⁰⁰, which produce proteases, most notably MMPs, such as collagenases and stromelysins¹⁰¹. In situ hybridization and immunohistochemistry studies show that the gene and protein levels of these enzymes are markedly higher in the synovial lining from patients with RA than in those with osteoarthritis, a joint disorder caused mainly by mechanical factors with little inflammatory involvement. High expression is also observed at the site of direct cartilage invasion in the pannus (a term describing the invasive and destructive front of synovial tissue attached to the articular surface). Endogenous MMP inhibitors are also expressed but are insufficient to block bone destruction¹⁰¹.

The phenotype of the FLS is aggressive in RA, which contributes to local matrix destruction¹⁰². This behaviour is maintained for many months if these cells are isolated from their local environment and transplanted in preclinical models. For example, FLS isolated from patients with RA invade aggressively into cartilage explants placed in immunodeficient mice, whereas FLS isolated from individuals with osteoarthritis or healthy controls or dermal fibroblasts do not degrade the matrix¹⁰³. The mechanism responsible for this behaviour is only partially understood. Abnormalities in the structure or regulation of genes encoding tumour suppressor p53 (TP53), sentrin-specific protease 1 (SENPI) and phosphatase and tensin homologue (PTEN) might contribute¹⁰⁴. Genes involved in many pathways

Box 1 | ACR/EULAR 2010 classification criteria for RA

The classification criteria proposed by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR)⁷³ include clinical and serological variables. The classification criteria should be restricted to individuals with ≥ 1 swollen joint. A score of ≥ 6 points is required for classification as definite rheumatoid arthritis (RA).

Joint involvement and distribution: 0–5 points

This variable includes any swollen or tender joint (excluding the distal interphalangeal joints of hands and feet, the first metatarsophalangeal joints and the first carpometacarpal joints) on clinical examination; additional evidence from MRI or ultrasonography may be used to identify additional joints.

- 1 large joint (shoulder, elbow, hip, knee or ankle): 0 points
- 2–10 large joints: 1 point
- 1–3 small joints (the metacarpophalangeal joint, the proximal interphalangeal joint, the second to fifth metatarsophalangeal joints, the interphalangeal joint of the thumb and the wrist): 2 points
- 4–10 small joints: 3 points
- >10 joints (of which ≥ 1 is a small joint^a): 5 points

Symptom duration: 0–1 points

This variable refers to the patient's self-report on the maximum duration of signs and symptoms of any joint that is clinically involved at the time of assessment.

- <6 weeks: 0 points
- ≥ 6 weeks: 1 point

Serology^b: 0–3 points

- Negative^c for RF and negative for ACPA: 0 points
- Low-positive^d for RF or low-positive for ACPA: 2 points
- High-positive^e for RF or high-positive for ACPA: 3 points

Acute-phase reactants^f: 0–1 points

- Normal CRP and ESR levels: 0 points
- Abnormal CRP levels or abnormal ESR: 1 point

ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor. ^aAdditional small joints include the temporomandibular joint, sternoclavicular joint, acromioclavicular joint and others, as reasonably expected in RA. ^bIf results of RF assays are only qualitatively available, a positive result should be scored as low-positive. ^cEqual or less than the upper limit of normal (ULN) for the respective laboratory. ^d >1 –3 times ULN. ^e >3 times ULN. ^fDetermined by local laboratory standards.

implicated in RA, such as cytokine signalling, cell adhesion and cell migration, are differentially methylated in FLS isolated from individuals with RA compared with those isolated from individuals with osteoarthritis, suggesting that FLS are imprinted and programmed for a more aggressive phenotype¹⁰⁵. Of interest, these marks can also vary on the basis of the joint of origin¹⁰⁵, suggesting a biological basis for asynchronous responses to targeted therapeutic agents.

Bone erosions are largely due to the maturation and activation of osteoclasts (bone-resorbing cells) (FIG. 3c) by receptor activator of nuclear factor- κ B (RANK; also known as TNFRSF11A) ligand (RANKL; also known as TNFSF11) produced by T cells, together with TNF, IL-6 and IL-1 produced by macrophages and FLS in the synovial lining¹⁰⁶. Osteoclasts can degrade the mineralized bone matrix by producing proteases, including cathepsin K, in a unique acidified local tissue microenvironment¹⁰⁷. It has also been suggested that ACPAs interact with citrullinated peptides (for example, citrullinated vimentin) expressed by osteoclasts and osteoclast precursors, leading to osteoclast maturation and activation, and, therefore, that ACPAs potentially initiate articular damage. Such interactions between the autoantibody and the osteoclast could precede the onset of synovial inflammation and provide novel mechanisms whereby autoantibodies, particularly ACPAs, contribute to tissue inflammation and remodelling beyond their traditional roles of complement activation^{108,109}. However, early, excessive osteoclast activation and severe joint damage also occurs in animals with TNF-driven arthritis in the absence of autoantibodies¹¹⁰.

Cytokine and signalling networks. Cytokine networks integrate pro-inflammatory and tissue-damaging cellular activities in synovitis (FIG. 2). The role of cytokines in disease pathogenesis was prominently established for TNF by the advent of TNF-targeting agents on the

basis of prior studies elucidating a pro-inflammatory role for TNF in leukocyte activation, MMP production, angiogenesis and promoting pain. Later studies targeting other cytokines, notably IL-6, demonstrated that the hierarchy of cytokines in patients with RA varies widely.

Synovial cells produce cytokines that act in a paracrine or autocrine fashion and can enhance and perpetuate inflammation in RA (FIG. 2c). For example, macrophages produce cytokines that activate adjacent FLS, T cells and dendritic cells. These cells in turn produce additional cytokines that can activate other cells in the joint environment. ACPA-induced IL-8 release from osteoclasts might play a particularly important part in early disease by driving neutrophil recruitment to the synovial fluid and activating and triggering subsequent responses¹⁰⁹. Thus, autonomous feedback loops ensure continuous recruitment of new cells and thereafter maintain cellular activation and immune effector function and limit apoptosis within the microenvironment. Although endogenous inhibitors such as IL-1 receptor antagonist protein (IL1RA; also known as IL1RN), soluble TNF receptors, IL-10 and IL-35 are also produced locally by macrophages, neutrophils and/or fibroblasts, the levels are insufficient to mitigate the inflammatory response¹¹¹.

The cytokine network hypothesis led to the introduction of successful therapeutic agents that target IL-6 and TNF. By contrast, IL-1 and IL-17 inhibitors were less successful, which is indicative of the challenge in selecting the pivotal cytokines amidst complex networks. Neutralizing antibodies to granulocyte-macrophage colony-stimulating factor are effective in clinical trials, indicating a further role for this cytokine in RA, but these antibodies are not yet approved^{112,113}.

Many cytokines, including IL-6 family members, interferons and γ -chain signalling cytokines such as IL-15 and IL-7, signal through Janus kinases (JAKs) after binding to their surface receptors. JAK inhibitors, especially JAK1 inhibitors, prevent activation of the signal transducer and activator of transcription (STAT) transcription factors in the synovium and are effective RA therapeutics¹¹⁴. Synovial biopsy studies show that the decrease in phosphorylated STAT1 and STAT3 by the JAK inhibitor tofacitinib correlates with clinical improvement of RA¹¹⁵. STAT1 and STAT3 are activated by JAK1 and are intimately involved with IL-6 signalling. Numerous additional signalling pathways have been targeted with less success to date, including p38 mitogen-activated protein kinases (MAPKs), MAPK/ERK kinase (MEK), spleen tyrosine kinase, Bruton tyrosine kinase and phosphoinositide 3-kinase^{116,117}.

Thus, the long pathway that leads to established RA (FIG. 2) creates many opportunities for therapeutic intervention. The diversity of biological processes and responses to targeted agents suggests that the clinical phenotype of RA represents a final common pathway rather than a single entity¹¹⁸. Understanding how these varying mechanisms converge will enable the personalization of treatment more effectively than our current trial-and-error algorithm.

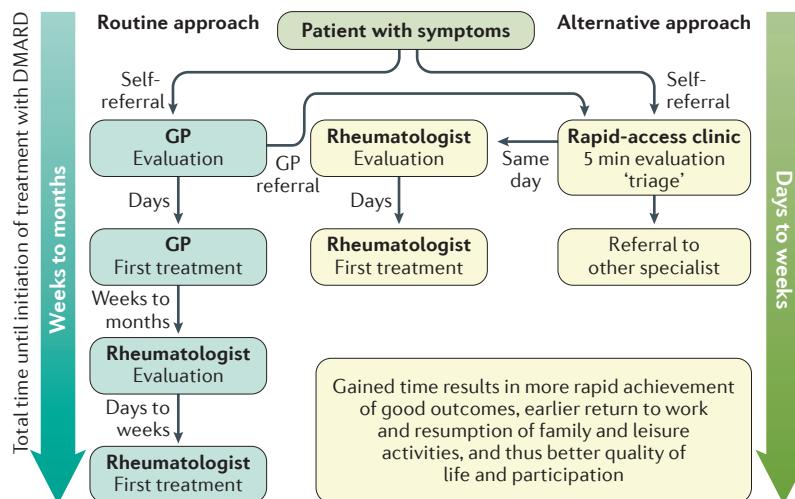


Figure 5 | Screening for rheumatoid arthritis. Rapid triage of patients very quickly after the onset of symptoms by an experienced rheumatologist enables early recognition and treatment initiation^{249,250}. DMARD, disease-modifying antirheumatic drug; GP, general practitioner.

Table 1 | Screening programmes in RA

Target population	Analysis	Outcome	Refs
Recruitment of individuals at health fairs with a first-degree relative with RA, joint pain or general arthritis concerns	Assessment of synovitis and ACPAs	<ul style="list-style-type: none"> • 1.5% of individuals had diagnosable RA at the time of screening • 2.5% of individuals had early inflammatory arthritis with synovitis and were autoantibody positive 	252
Recruitment of unaffected first-degree relatives of patients with RA	<ul style="list-style-type: none"> • Full examinations to rule out inflammatory arthritis • Genotyping • Serological testing 	<ul style="list-style-type: none"> • Genetic analysis alone identified that 9% of screened individuals were at very high risk of developing RA • 5% of screened individuals were autoantibody positive • 51% of screened individuals were at higher-than-normal risk ($\geq 5\%$ lifetime risk) of developing RA on the basis of a personalized risk calculator that comprises the factors age, sex, family history and risk-related behaviour (smoking, obesity, fish consumption and oral health) 	253, 254
Self-referral or referral by a clinician (non-rheumatologist)	Establishment of a 'rapid-access clinic' for a very brief (usually 5–10 min) first assessment by a senior rheumatologist with same-day referral if needed	<ul style="list-style-type: none"> • Reduction of waiting time to see a rheumatologist • Improved patient care by assuring quick assessment and referral • Earlier diagnosis • Earlier treatment 	249, 250

ACPA, anti-citrullinated protein antibody; RA, rheumatoid arthritis.

Diagnosis, screening and prevention

Diagnosis

Diagnosing RA is a highly individualized process led by the rheumatologist. Although no diagnostic criteria exist, classification criteria that include clinical manifestations and serological assays (autoantibody and acute-phase reactant levels) inform clinical diagnosis. Algorithms can be used for the diagnostic work-up of patients who present with arthritis and might lead to a specific diagnosis or to a diagnosis of undifferentiated arthritis.

Joint manifestations. Soft synovial joint swelling is the key clinical feature of RA and is typically accompanied by morning stiffness and tenderness on examination. Typical examples of patients with early, established and late RA are shown in FIG. 4a–f. Today, such dramatic evolution of the disease, which severely compromises mobility and can even lead to the need of a wheelchair or a bed-ridden state, is rarely seen owing to early diagnosis and better therapeutic options.

The joints involved in RA are quite specific and distinct from the types of involvement in other joint disorders, including the metacarpophalangeal joints and proximal interphalangeal joint of the hands and feet, and the wrist, ankle, elbow, shoulder, knee and hip joints¹¹⁹. Although all peripheral joints can be involved, the absence of RA in the distal interphalangeal joints and in the axial joints is striking. The single most important exception to this is the involvement of the C1–C2 joint of the spine (FIG. 4g). RA also distinguishes itself from other forms of arthritis by its highly destructive nature, which leads to inflammatory degradation of cartilage and destruction of articular and periarticular bone.

Despite these typical findings, many disorders mimic RA, which makes a differential diagnosis difficult, particularly in early disease. These disorders include

viral arthritis, Lyme arthritis, connective tissue disease, peripheral spondyloarthritis, psoriatic arthritis, osteoarthritis and metabolic diseases.

Systemic manifestations. RA does not exclusively affect the joints. As a systemic disease, RA is associated with an increased acute-phase response and can lead to a number of extra-articular manifestations in the eyes, lungs, heart and other organs. Rheumatoid nodules and vasculitis (FIG. 4h) might be observed in severe RA, although they are less common nowadays. However, cardiovascular disease is common in RA, and the incidence of interstitial lung disease has even been reported to have increased over time, with the incidence estimated at 4 cases per 1,000 individuals per year in 2010 (REF. 120). Although the increase in interstitial lung disease may be credited to an increased awareness and some detection bias over time, interstitial lung disease is — next to cardiovascular disease — one of the most severe extra-articular manifestations of RA, with an average patient survival of ~3 years¹²¹. RA may also be accompanied by secondary Sjögren syndrome; the chronic inflammatory process may lead to cardiovascular disease, secondary amyloidosis and lymphoma. RA can also be accompanied by fibromyalgia. Extra-articular manifestations and complications of disease may all be attenuated or reduced with effective treatment^{122,123}.

Classification criteria. The reasons for the lack of diagnostic criteria for RA are not only the interindividual and intra-individual heterogeneity of the disease but also the potential consequences of misdiagnosis. As for most other rheumatological conditions, only classification criteria are available⁷³ (BOX 1). Classification criteria are intended to stratify patients with similar characteristics for clinical research but do not intend to capture all patients; the high specificity but low sensitivity

Table 2 | Selected pharmacological prevention trials in RA

Study	Intervention	Duration: n	Study population	Results
PROMPT ^{133,255}	MTX (weekly oral administration) versus placebo	12 months; n=110	Undifferentiated arthritis, defined as symptoms of inflammatory arthritis for <2 years without meeting classification criteria for RA	RA development in 40% of the MTX group versus 53% of the placebo group ($P<0.05$)
PRAIRI ²⁵⁶	Rituximab (one i.v. administration) versus placebo	24 months, n=81	Either presence of arthralgias plus presence of ACPAs and/or rheumatoid factor and increased acute-phase reactant levels or presence of synovitis on MRI	RA development was 34% in the rituximab group and 40% in the placebo group ($P>0.05$); time to diagnosis of 25% of patients was 24 months in the rituximab group versus 12 months in the placebo group ($P>0.05$); nonsignificant difference suggests a delay rather than prevention of RA
DINORA ²⁰²	IFX plus oral MTX versus MTX alone or placebo	12 months (plus 12-month extension); n=90	Synovitis for 12–16 weeks in >1 joint	Stringent clinical remission at 12 months in 32.4% of those on IFX + MTX versus 14.3% for those on MTX alone and 0% for those on placebo ($P<0.05$ across the three groups); 25% of patients on IFX + MTX but 0% on MTX alone experienced remission at 2 years
ADJUST ²⁵⁷	Abatacept (for 6 months) versus placebo	12 months; n=24	Adults with undifferentiated RA meeting exactly 1 of the 1987 ACR criteria for RA classification ²⁵⁸	RA development was delayed but not prevented
STOP-RA ²⁵⁹	Hydroxychloroquine (daily) versus placebo	12 months n=200 ^a	High levels of ACPAs	Enrolling

ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; IFX, infliximab; i.v., intravenous; MTX, methotrexate; RA, rheumatoid arthritis.

^aTargeted enrolment.

distinguishes classification criteria from diagnostic criteria. Although they are meant to identify patients for clinical studies and trials, they might be used to inform diagnostic decision making in clinical practice, whereby a positive classification may also be associated with a negative diagnosis and vice versa. The difference between diagnostic criteria and classification criteria has been detailed extensively elsewhere¹²⁴.

The current classification criteria are those by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) established in 2010 (REFS 73,124) (BOX 1). Importantly, when using classification criteria, the target population must be adhered to, particularly when applying them to support diagnosis in clinical practice¹²⁵. The ACR/EULAR 2010 criteria have been developed for a target population of individuals presenting with at least one clinically swollen joint that cannot be clearly explained by another disease.

Undifferentiated arthritis. Important in the context of the later discussion on prevention is the concept of undifferentiated arthritis (that is, when a diagnosis of RA cannot be established despite the presence of one or more suggestive clinical findings). An algorithm for approaching these patients has been proposed, suggesting a full history and physical examination in all patients with indicative symptoms and who, most likely, have clinical arthritis¹²⁶. After exclusion of trauma and acute inflammatory events (such as gout, pseudogout or septic arthritis), a specific diagnosis may be established in the presence of suggestive clinical, laboratory or imaging features. The respective differential diagnoses will vary according to the number of swollen joints involved. Only if after careful work-up no specific diagnosis can be made (RA or any other definable

disease) can the presentation be labelled undifferentiated arthritis. Whether undifferentiated arthritis is a diagnosis or a descriptive term is a matter of debate, but patients who qualify as such need periodical re-evaluation, as undifferentiated arthritis may often just present a transition between health and a specific and definable disease.

Screening

Screening for RA involves the identification of disease at a time when patients are still asymptomatic and presents substantial challenges. Although RA is the most common autoimmune inflammatory arthritis, it remains relatively rare. Screening and prevention assume that patients with very early or preclinical RA can be accurately identified and that there are proved prevention strategies; alas, this is not feasible at the present time.

Identification of individuals with preclinical RA. Variables useful in screening for preclinical RA include genetic, serological, environmental and lifestyle factors (mainly smoking and periodontal disease). More than 100 genetic risk variants for RA have been identified thus far¹²⁷, but scoring systems based on genetics demonstrate only a modest increase in the risk of developing RA²². Thus, the use of genetics to assess the risk of developing RA is limited. Serological biomarkers, such as autoantibodies, enable the identification of people at increased risk of developing RA. Two-thirds of individuals ultimately diagnosed with RA were positive for ACPAs 6–10 years before their diagnosis¹²⁸. However, although the presence of ACPAs identifies a group of individuals at significantly increased risk of developing RA, the population prevalence (that is, pre-test probability) of RA is low, the positive predictive value is moderate (~70%) and about 2–5% of the healthy population

have ACPAs. Thus, the probability of developing RA in unselected ACPA-positive people (that is, post-test probability) can be estimated at only 50%. The post-test probability might be increased with very high titres of ACPAs or by combining RF and ACPAs.

Screening programmes. Screening programmes¹²⁹ have often targeted primary care physicians or nonphysician care providers (such as nurses or pharmacists) who can recognize patients yet to be diagnosed with RA who may have early inflammatory arthritis. Screening programmes for early inflammatory arthritis have targeted different populations and used various strategies¹³⁰ (FIG. 5; TABLE 1). These programmes have reduced times to diagnosis and treatment. Within 1 year, approximately one-third of patients fulfil criteria for RA, with another 5% meeting the criteria in the subsequent year¹³¹. Predictors of fulfilling classification criteria include the involvement of many joints at presentation, female sex, older age, presence of autoantibodies, acute-phase reactants and morning stiffness¹³².

Prevention

Prevention programmes are mainly aimed at individuals with undifferentiated arthritis and encompass risk factor modification and pharmacological strategies. Smoking cessation and/or oral health programmes might prevent some cases of RA without incurring risk. Other risk factor modification strategies proposed include increased fish consumption and weight loss. However, none of these strategies have been proved, and we are unaware of any active prevention trials targeting these factors.

Several trials to test strategies for RA prevention using drugs have been completed recently or are actively enrolling (TABLE 2). These selected RA prevention trials have raised several interesting issues. First, should the prevention strategy be a one-time dosage or chronic? If the treatment must be pursued chronically, it needs to have a very favourable benefit-to-risk ratio and cost should be considered. One might even ask if chronic preventive treatment is any different than chronic treatment. Second, what is the proper disease stage at which to target preventive treatment? Different treatments might be more appropriate for different stages (FIG. 1).

Finally, according to the re-analysis of the PROMPT trial¹³³, high-risk patients should be targeted to observe the greatest benefits of preventive treatment.

Management

The dramatic improvement in outcomes of RA is the consequence of several paradigm shifts over the past two decades. First, rheumatologists learned how to use the immunosuppressant methotrexate optimally, and this drug has become the therapeutic anchor for managing RA^{134–136}. Second, reliable instruments for clinical assessment have been developed that can be used for research and clinical practice^{137–139}. Third, early diagnosis and prompt initiation of effective therapy have become mandatory^{140–142}, have replaced earlier tardy approaches¹⁴³ and have led to new classification criteria that involve early RA patients⁷³. Fourth, remission (or at the very least targeting low disease activity) is now the aim of therapy in conjunction with tight control of clinical symptoms and prompt treatment adaptation in a treat-to-target approach^{144–147}. Finally, biological agents have entered the field of RA, providing the best effectiveness in combination with methotrexate^{148,149}. The combination of all these advances has considerably improved treatment outcomes for the majority of patients¹⁵⁰. However, not all patients can achieve low disease activity, let alone remission, and improvements are still required.

Treat-to-target strategy

The current treatment strategy for RA involves a treat-to-target approach based on tight monitoring of disease activity and change of management if a treatment target is not reached^{144,151,152}. This treat-to-target approach has been adopted by ACR, EULAR and the Asia Pacific League of Associations for Rheumatology in their management recommendations^{153–155}.

The current treatment goal is disease remission (or at the very least a low disease activity), which normalizes physical function when achieved in early disease and maximizes physical function in established disease; moreover, remission prevents occurrence of damage, or if joint destruction is present, its progression^{156,157}. Any new treatment should convey at least a

Table 3 | Disease activity measures used for RA

Scoring system	Formula	Disease activity states			
		Remission	Low disease activity	Moderate disease activity	High disease activity
SDAI	SJC28 + TJC28 + PGA + EGA + CRP	≤3.3	>3.3–11	>11–26	>26
CDAI	SJC28 + TJC28 + PGA + EGA	≤2.8	>2.8–10	>10–22	>22
DAS	Complex formula including the Ritchie index, SJC44, ESR and GH	≤1.6	>1.6–2.4	>2.4–3.7	>3.7
DAS28	Complex formula including the TJC28, SJC28, ESR (or CRP) and GH	≤2.6	>2.6–3.2	>3.2–5.1	>5.1

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein (in SDAI in mg per dl); DAS, Disease Activity Score; DAS28, DAS using 28-joint counts; EGA, Evaluator Global Assessment (on a 0–10 cm scale); ESR, erythrocyte sedimentation rate; GH, global health (that is, patient global assessment); PGA, patient global assessment (on a 0–10-cm scale); RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; SJC, swollen joint count (the number indicates the number of joints taken into account); TJC, tender joint count (the number indicates the number of joints taken into account).

50% improvement in disease activity within 3 months¹⁵⁸, and the treatment target should be reached within the subsequent 3 months. If not, treatment should be adapted or changed, but this decision will be made on an individual basis; treatment will not be escalated if the treatment target is nearly fulfilled or comorbidities or other safety issues preclude such a step.

Although the treat-to-target strategy is effective, clinicians frequently do not adhere to this strategy, mentioning time and resource constraints as the major obstacles¹⁵⁹. In addition, because treat-to-target strategies require shared decision making with the patient and patient adherence^{160–162}, learning initiatives and awareness programmes should be established to improve physicians' performance¹⁶³. An effective treat-to-target approach relies on frequent monitoring of disease activity and prompt treatment adaptations, as discussed below.

Measuring disease activity

RA is neither a metabolic disease, such as diabetes mellitus, in which laboratory measures reflect severity, nor a disease in which a blood pressure device can monitor the effectiveness of therapy; rather, its pathogenesis is complex, and it may be difficult to ever find a reliable biomarker to monitor disease severity that goes much beyond nonspecific tests for an inflammatory response. At present, the best biomarker that can be used to monitor disease severity is clinical disease activity¹⁶⁴. However, comorbidities, including fibromyalgia and other pain syndromes, should be taken into account when using any measure of disease activity¹⁴⁷.

CDAI and SDAI scores. Disease activity can be effectively assessed by the Clinical Disease Activity Index (CDAI) or the Simplified Disease Activity Index (SDAI). SDAI and CDAI remission constitute ACR and EULAR index-based remission definitions¹⁴⁶.

Box 2 | ACR improvement criteria

The American College of Rheumatology (ACR) improvement criteria are used to determine response to treatment; a treatment either reaches the level of improvement (positive response) or not (negative response). The criteria rely on improvement compared with baseline in the core set of disease activity measures mentioned below. The requirements for a respective response are:

- Improvements in swollen and tender joint counts, and
- Improvements compared with baseline values in three of the following five variables: patient global assessment, physician global assessment, patient pain assessment, physical function or quality of life score and acute-phase reactant levels (C-reactive protein or erythrocyte sedimentation rate)

An improvement of 20% (ACR20) is the minimal required response and implies that a 20% improvement in tender or swollen joint counts and a 20% improvement in at least three out of the five criteria is achieved.

Improvements of 50% and 70% (ACR50 and ACR70 responses, respectively) are the corresponding reductions from baseline in the above variables.

The SDAI and CDAI use a simple summation of several variables without weighting or transformation (TABLE 3). Remission, which relates to a state of no, or, at most, minimal disease activity, is the main target in early RA and corresponds to a CDAI score of ≤ 2.8 or an SDAI score of ≤ 3.3 (TABLE 3). Although these cut-off points should also be targeted in established RA, this is not always feasible, and low disease activity (CDAI of >2.8 –10 or SDAI of >3.3 –11) constitutes an alternative target¹⁴⁷. In patients with active RA, disease activity should be assessed every 1–3 months depending on the level of activity. Once the desired treatment target is achieved, less frequent follow-up (every 6–12 months) is sufficient.

DAS scores. Other scores that reflect general disease activity on a continuous scale are the Disease Activity Score (DAS) and its modification using only 28-joint counts (DAS28)^{165,166}. Their cut-off points for various disease states are shown in TABLE 3. Importantly, both DAS and DAS28 scores transform and weigh their component variables, resulting in a stronger influence of tender than swollen joints and a very high contribution of acute-phase reactant levels to the score, even within their normal ranges^{167,168}. There are two consequences of these transformations and weightings. First, in so-called remission, many swollen joints can be present, possibly leading to progression of damage in light of the association of damage with swollen rather than tender joint counts¹⁶⁹. Second, when drugs that interfere directly with acute-phase reactant synthesis, such as IL-6, IL-6R or JAK inhibitors, are used, exaggerated remission rates occur, which suggest wrongly that these drugs are more effective than others whereas this difference is simply an artefact of the formula^{128,170}. Indeed, in such situations, remission rates are always higher than ACR70 response rates and sometimes even higher than ACR50 response rates (see below)¹⁷¹, which disqualifies the term remission. Lowering the cut-off points for DAS28 remission does not help¹⁷², as the difficulty is in the construction of the formulae.

Boolean remission criteria. The ACR and EULAR have defined Boolean remission criteria, which include a swollen joint count of ≤ 1 , a tender joint count of ≤ 1 , a patient global assessment of ≤ 1 cm and a C-reactive protein level of <1 mg per dl (REF. 146). Boolean remission criteria are frequently not achieved because, due to past joint damage or secondary changes, the pain assessment by the visual analogue scale is >1 cm, whereas inflammation might have ceased¹⁷³.

ACR improvement criteria. In clinical trials, the clinical response is usually measured using ACR improvement criteria¹³⁷ (BOX 2), although changes in DAS28, SDAI and CDAI as well as low disease activity and remission states are increasingly applied. A 20% improvement (ACR20) is the minimal response and discriminates well between active treatment and placebo; ACR20 amounts to a 50% reduction in the SDAI (or CDAI)

Box 3 | Disease-modifying antirheumatic drugs for RA

Disease-modifying antirheumatic drugs (DMARDs) are listed per target.

Synthetic DMARDs*Conventional synthetic DMARDs*

- Unknown target: methotrexate, sulfasalazine, chloroquine, hydroxychloroquine and gold salts
- Known target: that is, dihydroorotate-dehydrogenase for leflunomide

Targeted synthetic DMARDs

- Janus kinase 1 (JAK1) and JAK2: baricitinib
- JAK1, JAK2 and JAK3: tofacitinib

Biological DMARDs*Biological originator DMARDs*

- Tumour necrosis factor: adalimumab, certolizumab, etanercept, golimumab and infliximab
- IL-6 receptor: tocilizumab and sarilumab
- IL-6^a: clazakizumab, olokizumab and sirukumab
- CD80 and CD86 (involved in T cell co-stimulation): abatacept
- CD20 (expressed by B cells): rituximab

Biosimilar DMARDs

DMARD nomenclature developed in 2013; list based on REF. 246. ^aNot yet approved or not further pursued (sirukumab). CD, cluster of differentiation.

score. Moderate improvement is based on a 50% improvement (ACR50) and relates to a 70% reduction in the SDAI (or CDAI) score, whereas a 70% improvement (ACR70) constitutes a major response, is compatible with most patients arriving at the level of low disease activity and relates to an 85% reduction in the SDAI (or CDAI) score¹⁷⁴. As these response criteria define the respective minimal cut-off point and include patients who have better responses, the overall mean response is much higher at the group level. However, ACR improvement criteria are not used in clinical practice because they are applied irrespective of baseline disease activity, do not reflect a particular disease activity level and cannot be used to determine a disease activity state (except an ACR100, which would reflect very stringent remission).

DMARDs

Interference with the inflammatory process requires DMARDs (BOX 3), among which synthetic DMARDs (that is, small chemical drugs) are distinguished from biological DMARDs (that is, monoclonal antibodies or, less often, receptor constructs). Biological DMARDs target soluble extracellular and cell-membrane-associated proteins with high specificity. Synthetic DMARDs can be separated into conventional synthetic agents (such as methotrexate), the modes of action of which are mostly unknown, and targeted synthetic DMARDs, which were developed to target specific molecules within cells. Biological DMARDs can be biological originator or biosimilar DMARDs. Biosimilars, if approved by the European Medicines Agency or the US FDA, can be regarded as equivalent in effectiveness and safety to the originator products, especially given the substantial batch-to-batch variation of the biological originator DMARDs^{175,176}.

Symptomatic agents, such as pain medications or NSAIDs, improve signs and symptoms but do not modify the underlying process and consequently do not interfere with the mechanisms leading to joint damage, although they relieve pain and swelling usually due to inhibition of prostaglandin synthesis¹¹³. Glucocorticoids do have disease-modifying activity, but their adverse effects preclude long-term use. However, given their rapid anti-inflammatory activity, they can be given for a limited period together with conventional synthetic DMARDs until the latter have exerted their full anti-inflammatory potential (the concept of ‘bridging’)¹¹³.

Methotrexate and glucocorticoids. The 2016 update of the EULAR management recommendations for RA suggests starting treatment with methotrexate plus short-term glucocorticoids¹⁵³. Methotrexate should be rapidly escalated to the optimal dose (25 mg once weekly) with folate substitution to mitigate or prevent adverse events without interfering with effectiveness. Of note, in contrast to the anti-proliferative effects of methotrexate, which occur at much higher doses than used in RA, the anti-inflammatory effects of methotrexate do not involve the folate pathways¹³⁶.

Glucocorticoids (for example, oral prednisolone) should be given at a low dose¹⁷⁷ or intermediate dose¹⁷⁸ for a few weeks to a maximum of 4–5 months, when methotrexate (or another conventional synthetic DMARD) should have reached full effectiveness. A higher dose of prednisolone¹⁷⁸ might be required when patients have very active disease. Alternatively, a single intramuscular injection of depot methylprednisolone¹⁷⁹ or a single intravenous infusion of a high-dose prednisolone¹⁸⁰ at the start of methotrexate treatment may be used. Some clinicians feel that glucocorticoids could be used long-term at a low dose (for example, ≤5 mg prednisone daily). Indeed, data suggest that low-dose glucocorticoids do not lead to adrenal suppression¹⁸¹ and are not associated with recognized adverse events¹⁸². However, such views ignore that the cumulative dose of glucocorticoids is also associated with mortality¹⁸³. For this reason, the EULAR task force recommends using glucocorticoids only short-term for bridging at any dose¹⁵³.

All available data show that as a first treatment strategy, such as in early RA, the combination of methotrexate plus glucocorticoids leads to stringent remission in ~25% of patients within 6 months, with an additional similar or even higher proportion achieving a state of low disease activity. The results obtained with methotrexate plus glucocorticoids are neither surpassed by combining two to three conventional synthetic DMARDs^{178,179} plus glucocorticoids nor by using anti-TNF plus methotrexate therapy¹⁸⁰. When methotrexate cannot be used, alternative conventional synthetic DMARDs include sulfasalazine or leflunomide (BOX 3).

Insufficient response to methotrexate. When methotrexate plus short-term glucocorticoids conveys an insufficient therapeutic effect, stratifying patients by prognostic factors is recommended¹⁵³. Those without adverse prognostic factors (such as presence of autoantibodies,

high disease activity or early radiographic joint damage¹⁸⁴) may receive another conventional synthetic DMARD as monotherapy or added to methotrexate, again with a short course of glucocorticoids. Those who have adverse prognostic markers or who have failed two courses with conventional synthetic DMARDs¹⁸⁵ should receive a biological DMARD (parenteral treatment) or a targeted synthetic DMARD (oral treatment). Of note, because the experience with biological DMARDs is much greater than that with targeted synthetic DMARDs, EULAR recommendations currently express a preference for using a biological DMARD first¹⁵³.

The mechanisms of action of the biological and targeted synthetic DMARDs are depicted in FIG. 6. Intriguingly, although abatacept has been developed to target T cell co-stimulation, the lack of good efficacy of other anti-T cell therapies, such as anti-CD4¹⁸⁶ and anti-IL-17 (REF. 187), as well as the paucity of synovial T cells in established RA do not strongly support this concept; by contrast, abatacept might also interfere with macrophage migration, a pivotal event in RA pathogenesis¹⁸⁸. Similarly, how B cell depletion interferes with

RA pathogenesis is unclear¹⁸⁹, but reduction of autoantibody production, depletion of antigen-presenting cells or both might be involved.

All biological DMARDs and targeted synthetic DMARDs are more efficacious when combined with a conventional synthetic DMARD than as monotherapy^{153,190–193}. However, monotherapy with IL-6 receptor inhibitors has better efficacy than monotherapy with a TNF inhibitor, and monotherapy with JAK inhibitors is more effective than methotrexate monotherapy^{190,191}. Consequently, when conventional synthetic DMARDs are not tolerated, IL-6 receptor blockers or JAK inhibitors are preferred¹⁵³.

Various meta-analyses and head-to-head trials have revealed that when combined with methotrexate, all biological DMARDs and targeted synthetic DMARDs have a similar efficacy across essentially all end points studied, irrespective of their target^{190,190,194–196} (FIG. 7). This ceiling effect might be due to study design, patient selection or the metrics used for outcome assessment. However, a bottleneck hypothesis¹¹³ is more likely because, irrespective of the treatment target, all treatments aim to shut down TNF and/or IL-6 effects, which might explain the similarity of overall response rates (FIG. 6). Data of direct head-to-head trials of baricitinib (plus methotrexate) or toficitinib (plus methotrexate) compared with adalimumab (plus methotrexate) in patients with active disease despite previous methotrexate treatment have revealed similar response rates for toficitinib plus methotrexate^{193,197}, whereas baricitinib (plus methotrexate) was slightly but statistically significantly superior to adalimumab (plus methotrexate) for the primary end point (ACR20) and most other clinical end points¹⁹⁷. Whether this difference is clinically meaningful is a matter of debate.

Whether biological DMARDs should be used as the first-line strategy rather than conventional synthetic DMARDs (plus glucocorticoids) has been extensively debated in the field. However, thus far, no convincing data support this contention. Indeed, the number of methotrexate-naïve patients who respond to methotrexate is within the same range of the number of those who had an inadequate response to methotrexate and were receiving biological DMARDs in addition to their methotrexate (FIG. 7). However, the proportion of patients responding to methotrexate as a first DMARD plus the proportion of patients who respond to any biological DMARD after an insufficient response to methotrexate exceeds the proportion responding to biological DMARD plus methotrexate in methotrexate-naïve patients (FIG. 7). This finding was also clearly illustrated in the OPTIMA trial^{198,199}. This trial further revealed that joint damage does not progress in individuals with early RA who receive methotrexate if stringent remission is achieved; even in non-responders, the progression of damage is minimal after 6 months when therapy is re-evaluated^{198,200}. Thus, first-line biological DMARD use would lead to overtreating >25% of individuals with RA without added benefit and at high cost, and it does not seem to harm those who respond insufficiently to first-line methotrexate therapy.

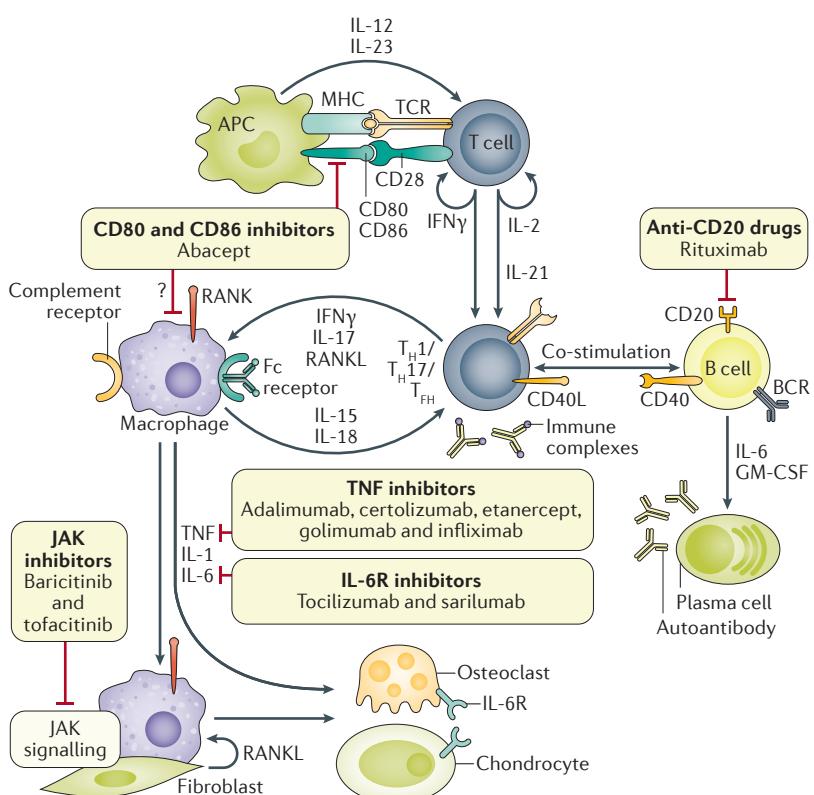


Figure 6 | Management of RA with disease-modifying antirheumatic drugs. Tumour necrosis factor (TNF) inhibitors, IL-6 receptor (IL-6R) inhibitors and Janus kinase (JAK) inhibitors block the action of the pro-inflammatory cytokines involved in the initiation and progression of rheumatoid arthritis (RA). Targeting upstream events (that is, with abatacept, rituximab) leads to a downregulation of these pro-inflammatory cytokines. The hypothesis of the ‘common final pathway’ may explain the similarity of treatment responses of all these therapies. APC, antigen-presenting cell; BCR, B cell receptor; CD, cluster of differentiation; CD40L, CD40 ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; MHC, major histocompatibility complex; RANK, receptor activator of nuclear factor- κ B; RANKL, receptor activator of nuclear factor- κ B ligand; TCR, T cell receptor; T_{FH} , T follicular helper cell; T_H , T helper cell.

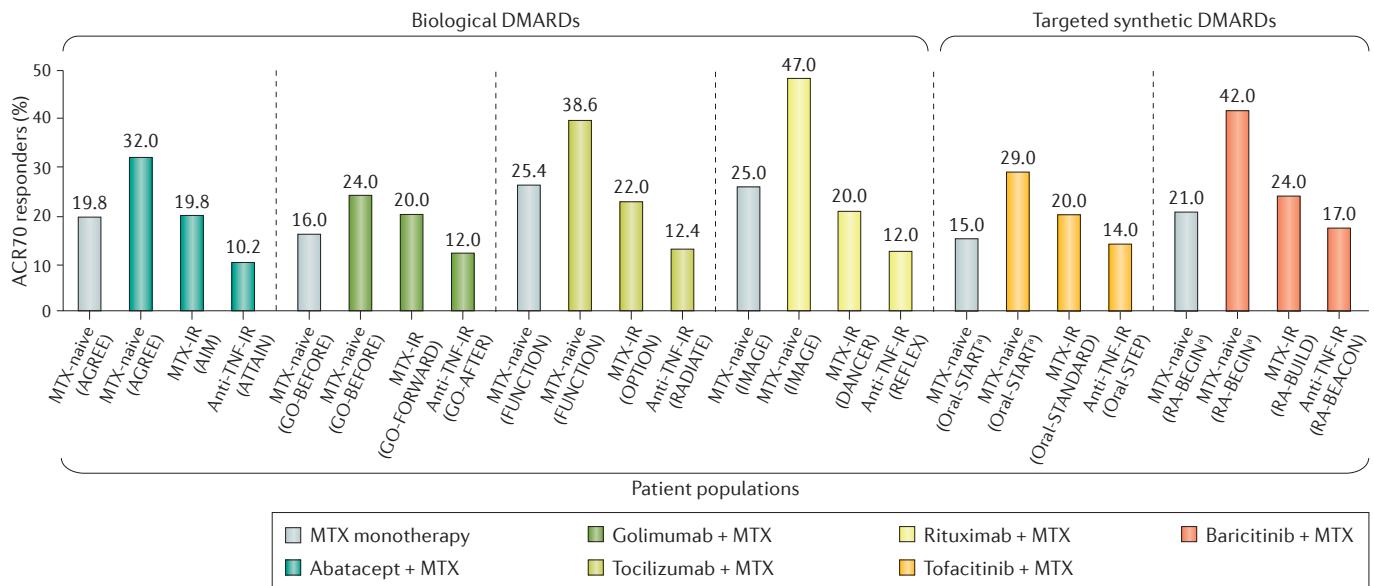


Figure 7 | Treatment response to disease-modifying antirheumatic drugs in RA. Treatment response measured by 70% improvement in the American College of Rheumatology (ACR) response criteria (ACR70) for methotrexate (MTX) and several biological and targeted synthetic direct-acting disease-modifying antirheumatic drugs (DMARDs) in three populations with rheumatoid arthritis (RA): individuals with RA who are MTX naive, who show an insufficient response (IR) to MTX or who experience failed anti-tumour necrosis factor (TNF) therapy (anti-TNF-IR). Please note that in MTX-naive RA patients, the response rates to MTX vary widely and response rates to various biologic DMARDs vary accordingly; this shows how the same drug (MTX) can act differently in various trials, even those with similar inclusion criteria. In contrast to MTX-naive patients, MTX-IR and anti-TNF-IR patients experience overall similar response rates to the various biological agents. These are data from published trials (in parentheses) and not head-to-head comparisons (the respective trials are referred to in REF. ¹¹³). Graph based on data presented in REFS ^{113,251}. ^aMonotherapy (without MTX).

Withdrawal of biological DMARDs is not routinely recommended, but after early remission induction, sustained biological-DMARD-free remission has been documented^{198,201,202}. If this could be replicated routinely, it might make a logical case for first-line biological DMARD use.

Non-responders. Non-response can be classified in those who never showed an adequate response to a certain drug (primary non-responders) or, more commonly, those whose response to treatment diminishes likely owing to development of anti-drug antibodies (secondary non-responders). In non-responders, another biological DMARD or a targeted synthetic DMARD is indicated. Although all biological DMARDs exhibit similar efficacy in clinical trials, the response rate decreases with increasing disease duration or multiple drug exposure. Indeed, patients who have active disease despite previous use of TNF inhibitors respond less well to other biological and targeted synthetic DMARDs than those who only failed methotrexate¹¹³ (FIG. 7). It is noteworthy that in those who insufficiently respond to anti-TNF agents, treatment with agents with another mode of action is not more effective than treatment with another TNF inhibitor²⁰³ (FIG. 7). In addition, regarding primary non-responders, certolizumab was effective in adalimumab primary non-responders and vice versa¹⁹⁶. Thus, although one would expect that an agent with a different mode of action is needed in non-responders, the use of a molecule with the same mode of action but

different immunogenicity often works well. However, more studies, especially in primary non-responders, are needed.

Targeted synthetic DMARDs show a numerically somewhat higher response than the biological DMARDs in patients who have previously failed biological DMARDs. No head-to-head trials among JAK inhibitors have been performed hitherto.

Biosimilars. One of the overarching principles of the EULAR recommendations mentions that rheumatologists also should consider the costs of therapeutic interventions¹⁵³. In line with WHO reports²⁰⁴, rational therapy comprises the right agent at the right dose and at the lowest cost to the individual and society. With the advent of biosimilars for biological originator DMARDs, the costs of treating RA in patients who have failed conventional synthetic DMARDs will considerably decrease, provided that the biosimilars are available at a much lower cost than the original compounds, which is currently the case in many countries but not, for example, in Germany, Romania and other countries¹⁷⁵. In a non-inferiority double-blind phase IV trial in a hospital setting, switching from an originator anti-TNF, infliximab, to an infliximab biosimilar across several diagnoses, including RA, was not inferior to continuation of originator infliximab, further substantiating the similarity of originator and biosimilar compounds²⁰⁵. The use of biosimilars in RA has been reviewed elsewhere²⁰⁶.

Table 4 | Adverse events associated with DMARDs

Drug or class	Adverse effects						Contraindications
	Dermatological	Gastroenterological	Haematological	Respiratory	Urogenital	Other	
Conventional synthetic DMARDs							
MTX ²⁶⁰	Stomatitis (inflammation of the mucosa of mouth and lips) and alopecia	Nausea, vomiting and increase in liver enzymes, usually without clinical effects on liver function	Leukocytopenia, macrocytic anaemia and thrombocytopenia	Pneumonitis and atypical pneumonia	Oligospermia and kidney function impairment	Fever, headache, depression and rheumatoid nodules	<ul style="list-style-type: none"> • Impaired kidney function (if so, LEF should be used) • Before conception or during pregnancy
SSZ	Exanthema, pruritus and, rarely, EEM syndrome, Stevens–Johnson syndrome, Lyell syndrome and photosensitivity	Nausea, abdominal pain, diarrhoea, cholestasis, hepatitis and pancreatitis	Hyperchromia, thrombocytopenia, leukopenia (rare: agranulocytosis) and methemoglobinemia or sulfhemoglobinemia	Not observed	Oligospermia (reversible), proteinuria and nephritis	Headaches, fatigue, polyneuropathy, depression, psychosis and drug-induced lupus erythematosus	Hypersensitivity to sulphonamides or salicylates
LEF ²⁶¹	Eczema, alopecia, rash, urticaria, pruritus and, very rarely, Steven–Johnson syndrome	Diarrhoea, nausea, vomiting, oral ulcers, abdominal pain and increase in liver enzymes	Leukocytopenia, anaemia and, very rarely, pancytopenia	Interstitial lung disease	Not observed	Hypertension, dizziness, headaches, polyneuropathy and weight loss	Before conception or during pregnancy
Biological DMARDs							
TNF inh	Reaction at the injection site, rash, cellulitis and psoriasis	Increase in liver enzymes	Leukocytopenia and thrombocytopenia	Infections, pneumonia, tuberculosis and opportunistic infections	Urogenital tract infection	Demyelination and systemic lupus erythematosus-like syndrome	Active or chronic infections including untreated tuberculosis, current malignancy, demyelinating diseases such as multiple sclerosis, hypersensitivity to drug class or severe heart failure
TOC or SAR	Reaction at the injection site and cellulitis ^a	Hyperlipidaemia, increase in liver enzymes, diverticulitis ^a and lower intestinal perforations ^a	Neutropenia	Infections ^a and pneumonia ^a	Not observed	Hypersensitivity reaction	Active or chronic infections, including untreated tuberculosis, hypersensitivity to drug class or diverticulitis
ABT	Rash and herpes infection	Abdominal pain, nausea, dyspepsia, diarrhoea and hyperlipidaemia	Leukopenia and thrombocytopenia	Bronchitis, cough and infections	Urogenital tract infection	Fatigue, weight loss, hypertension, headaches and nausea	Active or chronic infections, including untreated tuberculosis and hepatitis B, current malignancy or hypersensitivity to drug class
Rituximab	Hypersensitivity reactions	Dyspepsia and reactivation of hepatitis B	Leukopenia and pancytopenia	Infections and bronchial spasms	Not observed	Infusion reactions (rarely, anaphylaxis), temporary hyperuricemia, myocardial insufficiency and, rarely, PML	Active or chronic infections, hepatitis B or hypersensitivity to murine proteins

This table is not comprehensive. It was compiled from the monitoring recommendations of the German Society of Rheumatology (<https://dgrh.de/Start/Versorgung/Therapieüberwachung/Therapieüberwachungsbögen.html>) and the summary of product characteristics. ABT, abatacept; DMARD, disease-modifying antirheumatic drug; EEM, erythema exsudativum multiforme; LEF, leflunomide; MTX, methotrexate; PML, progressive multifocal leukoencephalopathy; SAR, sarilumab; SSZ, sulfasalazine; TNF inh, tumour necrosis factor inhibitor; TOC, tocilizumab. ^aLaboratory assessments of acute-phase reactants might be negative or low upon tocilizumab treatment.

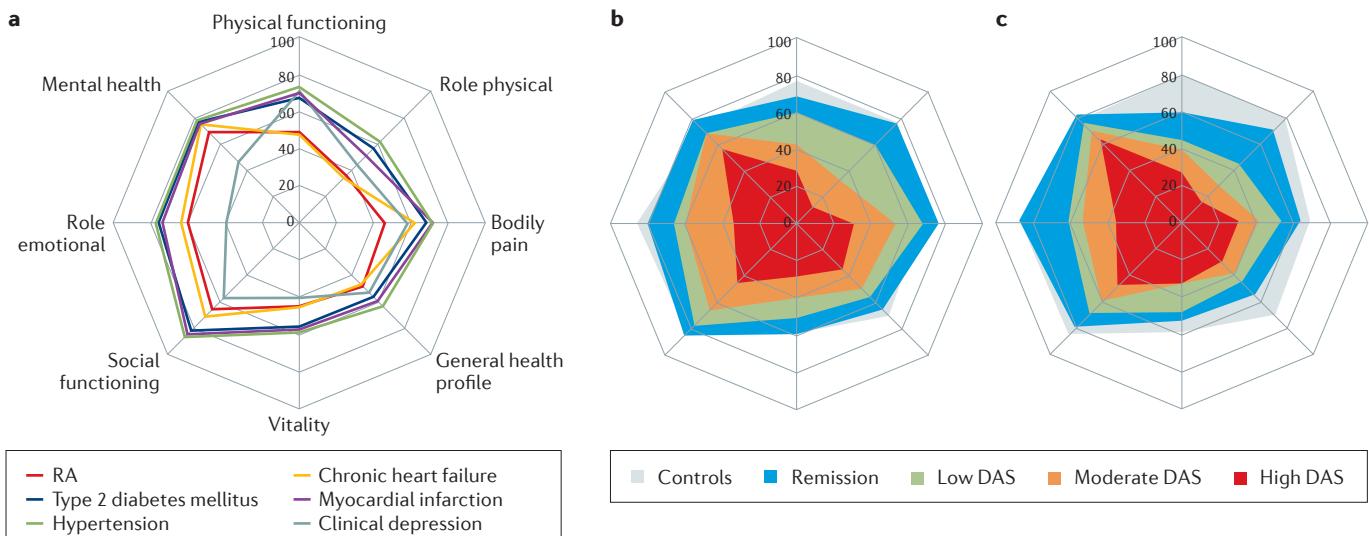


Figure 8 | HRQOL in individuals with RA. Spydergrams portraying the eight individual domain scores of the Medical Outcomes Survey Short Form-36 (SF-36), including physical functioning, role limitations due to physical pain (role physical), bodily pain, general health profile, vitality, social functioning, role limitations due to emotional problems (role emotional) and mental health. **a** | Health-related quality of life (HRQOL) in individuals with rheumatoid arthritis (RA) compared with that of individuals with other chronic conditions. **b** | The effects of intensive

treatment and remission on HRQOL in individuals with early RA in the CARDERA trial. **c** | The effects of intensive treatment and remission on HRQOL in individuals with established RA in the TACIT trial. Controls include data from age-matched and sex-matched individuals from the United Kingdom who do not have chronic diseases or RA; data from individuals with RA with different Disease Activity Scores (DAS) are also shown. Part **a** is adapted with permission from REF. 219, Elsevier. Parts **b** and **c** adapted from REF. 227, CC BY 4.0.

Adverse effects. Current management of RA also aims to reduce adverse effects, not only by taking the specific properties of the drugs into account but also by tailoring treatment to the patient by considering underlying comorbidities such as chronic kidney diseases, diabetes mellitus or previous infections. NSAIDs are used widely in RA. The traditional NSAIDs such as ibuprofen, naproxen and diclofenac also target cyclooxygenase 1 (COX1; also known as PTGS1) and can, therefore, lead to gastrointestinal events²⁰⁷ and affect coagulation when given in higher amounts over a longer period. Although the COX2-specific drugs celecoxib and etoricoxib usually do not cause these problems, all NSAIDs influence renal blood circulation and may lead to cardiovascular problems²⁰⁸. Thus, contraindications should be considered^{207,208}, and NSAIDs should primarily be given in the very early phase of RA to alleviate symptoms before specific antirheumatic treatment is initiated or at later time points when post-arthritis pain occurs.

Long-term use of glucocorticoids can have a broad spectrum of adverse effects, such as skin atrophy, osteoporosis, disturbed glucose tolerance, hypertension, elevated intraocular pressure, cataract development and a higher risk of infections²⁰⁹. Thus, glucocorticoids are usually given at moderate doses in the initial treatment phase with rapid tapering or later when flares occur at the lowest possible dose for the shortest time period possible.

The adverse effects associated with DMARDs are listed in TABLE 4. Overall, all biological DMARDs have a good benefit-to-risk profile, and the primary risk is infections, with a rate of ~4–5 events per 100 patient-years; the risk depends on underlying risk factors such as smoking, concomitant glucocorticoid treatment, age and

comorbidities²¹⁰. A calculator has been developed by the German RABBIT registry for easy risk assessment²¹¹. Registries demonstrate that biological DMARDs do not confer a higher risk of malignant diseases²¹². Specific properties of the individual biological DMARD classes include a risk of tuberculosis with TNF inhibitors (but the risk can be reduced by >80% using proper screening and pre-emptive treatment of latent tuberculosis²¹³), a risk of gastrointestinal perforations (2–3 events per 1,000 patient-years) with tocilizumab²¹⁴ and, very rarely, a risk of progressive multifocal leukoencephalopathy with rituximab treatment²¹⁵.

JAK inhibitors have a similar adverse effect profile as the biological DMARDs^{216,217} but carry a higher risk of herpes zoster virus reactivation, especially in Japanese and Korean individuals owing to a particular genetic profile involved in herpes zoster virus reactivation. Because targeted synthetic DMARDs are small chemical molecules, potential interactions with the cytochrome profile for metabolizing other drugs should be considered.

Quality of life

Health-related quality of life

RA profoundly affects health-related quality of life (HRQOL)²¹⁸. Compared with type 2 diabetes mellitus, myocardial infarction and hypertension, individuals with RA report lower Medical Outcomes Survey Short Form-36 (SF-36) domain scores; scores are comparable between individuals with RA and those with chronic heart failure²¹⁹ (FIG. 8a). RA reduces HRQOL in all physical and mental domains both in UK and US populations, with less reduction in mental health than in physical performance, although fatigue and depression are prevalent²²⁰.

Box 4 | Estimation of the cost of illness

The cost of illness includes direct costs (such as the costs of the medications and the monitoring required when using them), indirect costs (for example, loss of productivity, such as unemployment due to uncontrolled disease) and intangible costs (such as effects on pain and quality of life). Indirect costs, such as the loss of productivity, constitute a substantial part of the total cost in rheumatoid arthritis. Various aspects of productivity should be considered, including not only absenteeism (that is, economic costs of an employee missing work owing to their disease) but also presenteeism (that is, reduced productivity of an employee due to the disease while at work). A number of tools have been developed in an attempt to capture these factors²⁴⁷. Results vary depending on the tool used, and there is not a 'gold standard' at present.

Analysis of the effect of treatment of RA on HRQOL is based on 20 years of data collected from randomized controlled trials (RCTs), the majority of which included patient-reported outcomes such as patient global assessment of disease activity, pain, the Health Assessment Questionnaire Disability Index (HAQ-DI), the SF-36, the EuroQol-5 Dimensions (EQ-5D) instrument and measures of participation and work productivity. Registries established to monitor biological DMARD treatments and longitudinal observational studies have also included HRQOL measures^{221–226}. Together, these data have shown that HRQOL increases with improvement in disease activity²²⁷ (FIG. 8b,c). Data from the German RABBIT registry, among others, demonstrate that improvements in HRQOL are the largest after the first conventional synthetic DMARD therapy and the first biological DMARD therapy compared with subsequent therapies, with progressively lower pretreatment scores in relation to an increasing number of prior therapies²²⁸.

RCTs have confirmed that all DMARDs approved for treatment of RA since 1998 have resulted in significant improvements in patient-reported outcomes, including in SF-36 scores. Changes may be generally evident as early as week 1–2, are definitely evident within 3 months after treatment initiation in responders and are maintained or further improved thereafter^{229–231}. Minimum clinically important differences (improvements perceptible to patients) to evaluate effectiveness in RCTs have been defined as 2.5-point improvements in the SF-36 Physical Component Summary and Mental Component Summary or 5-point improvements in an individual domain score (0–100 scale)²³². These scores are similar to statistically defined minimum important differences, which are based on changes in standard deviations of ≥ 0.5 (REF. 233).

A systematic literature review and meta-analysis reviewed SF-36 scores reported in 31 longitudinal observational studies, including data from 22,335 patients. The pooled mean Physical Component Summary and Mental Component Summary scores were similar in these studies compared with those reported in RCTs^{219,234}. Nonetheless, improvements reported in longitudinal observational studies with standard of care, even when treatment is initiated or increased, are smaller than in RCTs, likely owing to expectation bias on behalf of both patient and physician^{234–236}.

Several HRQOL instruments have been developed that can be used in clinical practice. The RA Impact of Disease Scale (RAID) has been validated in RCTs but

can also be easily used in the clinical setting^{237,238}. The Routine Assessment of Patient Index Data 3 (RAPID3) score and the Multidimensional Health Assessment Questionnaire (MDHAQ) include patient global assessment and pain, both on 100 mm visual analogue scales, and a measure of physical function (measured by modified HAQ (mHAQ), HAQ-DI or MDHAQ)²³⁹. These questionnaires do not query fatigue specifically, which is an important manifestation of RA, but pain, fatigue and limitations in physical activities are all reflected in the patient global assessment score included in the RAPID3 score. Another efficient means of assessing HRQOL in clinical practice is to set a specific goal with a patient when initiating a new therapeutic regimen that can be queried at each clinic visit as a means of monitoring response²⁴⁰.

Work capacity

If uncontrolled, RA is chronic and progressive and may lead to considerable joint damage, dysfunction, work disability and other sequelae that result in large economic losses. The economic burden of RA before the introduction of biological DMARDs is extensively analysed in the literature. A 2009 systematic review of 26 cost-of-illness or cost-effectiveness studies showed that the overall mean total cost of RA was approximately €14,906 per patient per year; indirect productivity costs constituted the largest part of the total cost²⁴¹. An analysis reported in 2008 showed that the total costs of RA to society were estimated at €45.3 billion in Europe and €41.6 billion in the United States²⁴².

To optimally assess the value of biological DMARDs, a comprehensive approach should be used considering all costs of illness (BOX 4). A systematic review of 10 studies on the effects of biological DMARDs on participation in paid work by individuals with RA noted that, compared with conventional synthetic DMARDs, employment status improved in 4 out of the 14 studies in which it was measured, but absenteeism improved in 10 of 10 studies and presenteeism improved in 7 of 9 studies²⁴³. Given the high acquisition costs of novel agents, some pharmacoeconomic analyses have suggested that the use of older agents can be cost-effective²⁴⁴. However, other economic analyses indicate that the superior clinical outcomes that may be achieved by biological agents may offset at least some of their high acquisition costs; the value of such therapy is affected by various aspects of the analyses and ultimately depends on individual and local considerations. In addition, with the advent of biosimilars, the costs of biological DMARDs have already been reduced in most countries, with a reduction of up to 50% in some countries^{206,245}.

Outlook

As discussed in this Primer, our insights into the epidemiology, genetics, pathogenesis, clinical assessment and therapy of RA have reached a state that no one dreamed of 2 decades ago. RA has turned from a highly disabling disease for which no effective remedies existed to a disorder that can be controlled well, with many patients reaching remission.

There are still several unmet needs. First, although RA can be brought into remission (that is, a state of normality with drug treatment), we need to uncover the cause or causes of RA to attempt a cure or at least prevention, as speculative and aspirational as these goals may be. Second, some patients still do not reach low disease activity, let alone remission. Hence, we still are in need of additional therapies. Third, we are puzzled by the similarity of response rates to the various targeted therapies. This finding might be explained by a common pathway targeted by these DMARDs. If so, the pathogenesis of RA in non-responders might use a different, as yet unidentified, pathway. Alternatively, this phenomenon might be the consequence of a natural

limitation in responsiveness to treatment, given that across all therapies patients with the highest disease activity respond the least. Fourth, we still cannot predict by virtue of biomarkers who will respond best to which type of targeted treatment. Consequently, we are still relying on a trial-and-error approach, although we know that clinical improvement early in the course allows for the best clinical outcome. Thus, much more research is still needed to tie the genetic, epigenetic, environmental and therapeutic factors together to succeed in the quest for curative or preventive therapies, which remains a pivotal item on the agenda of basic and clinical scientists and, hopefully, will be achieved within the coming decade.

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Author contributions

Introduction (J.S.S.); Epidemiology (K.Y. and A.B.); Mechanisms/pathophysiology (I.B.M. and G.S.F.); Diagnosis, screening and prevention (D.A. and D.H.S.); Management (J.S.S., P.E. and G.R.B.); Quality of life (V.S. and A.K.); Outlook (J.S.S. and I.B.M.); Overview of Primer (J.S.S.).

Competing interests

J.S.S. has received grant support from and/or provided expert advice to AbbVie, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, Celltrion, Gilead, Glaxo, ILTOO, Janssen, Lilly, Pfizer, MSD, Roche, Samsung, Novartis-Sandoz and UCB. D.A. served as a consultant and/or speaker for AbbVie, AstraZeneca, BMS, Janssen, Medac, MSD, Pfizer, Roche and UCB and received grant support from BMS. A.B. received grants, speaker fees and/or consultancy fees from Pfizer, Eli Lilly, Janssen, Celgene, Roche-Chugai and Boehringer-Ingelheim. G.R.B. received honoraria for consulting and lectures from AbbVie, BMS, MSD, Pfizer, UCB and Roche. P.E. has undertaken clinical trials and provided expert advice to Pfizer, MSD, AbbVie, BMS, UCB, Roche, Novartis, Samsung, Sandoz and Eli Lilly. G.S.F. has received grant funding from Janssen and Gilead. A.K. has served as a consultant and/or performed clinical research for AbbVie, Amgen, Celgene, Janssen, Novartis and UCB. I.B.M. has received grants, speaker fees and/or consultancy fees from BMS, AbbVie, Pfizer, Eli Lilly, GSK, Janssen, Novartis, Celgene, Roche-Chugai, UCB and Boehringer-Ingelheim. D.H.S. serves in unpaid roles on a clinical trial sponsored by Pfizer. V.S. has served as a consultant to AbbVie, Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Celltrion, Genentech/Roche, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sanofi and UCB and is a founding member of the executive of OMERACT (Outcome Measures in Rheumatology: 1992–present), an organization that develops and validates outcome measures in rheumatology randomized controlled trials and longitudinal observational studies and receives arm's-length funding from 36 sponsors. K.Y. received honoraria for consulting and lectures from AbbVie, AYUMI, BMS, Chugai, Eisai, Janssen, Ono, Pfizer, Tanabe-Mitsubishi and UCB.

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