Rheumatoid arthritis: from palliation to remission in two decades

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ABSTRACT

The last 20 years have seen a transformation in the landscape of rheumatoid arthritis, which has changed from being a life limiting condition to a chronic but often remitting illness. The importance of early disease control, the better use of existing therapies, and the development of new therapies have all been key to this success. The future of therapy now lies in the identification of stratifying biomarkers, to allow more rational delivery of treatment. The ultimate goal remains the reintroduction of immune tolerance to potentially achieve a 'cure.'

KEYWORDS: Rheumatoid arthritis, biologics, biomarkers, stratified medicine, immune tolerance

Introduction

Rheumatoid arthritis (RA) is a common and debilitating autoimmune inflammatory disease. It is characterised by inflammation and destruction of synovial joints and has myriad extra-articular manifestations. From a historical perspective, RA typically follows a pattern of relentless progression to irreversible joint damage and disability. However, over the last 20 years there has been a transformation in patient outcomes, driven by new management strategies and an array of new therapies. It has now become the norm to achieve disease control, and in some cases drug free remission, rendering the joint deformities and disabilities of the past vanishingly rare.

Inflammation and outcomes in RA

The synovial inflammation seen in RA is an archetypal example of the inflammatory response. The normally thin sub-lining layer of the synovium is infiltrated by a rich milieu of immune and effector cells. These cells and their cytokine messengers are involved in the propagation of the inflammatory response and drive the effector cells to cause local cartilage damage and bone destruction[1] (Fig 1).

Authors: [A]academic clinical fellow, Musculoskeletal Research Group, Newcastle University, Newcastle-upon-Tyne, UK; [B]director of the Institute of Cellular Medicine and professor of clinical rheumatology, National Institute for Health Research Newcastle Biomedical Research Centre, Newcastle Hospitals NHS Trust and Newcastle University, Newcastle-upon-Tyne, UK

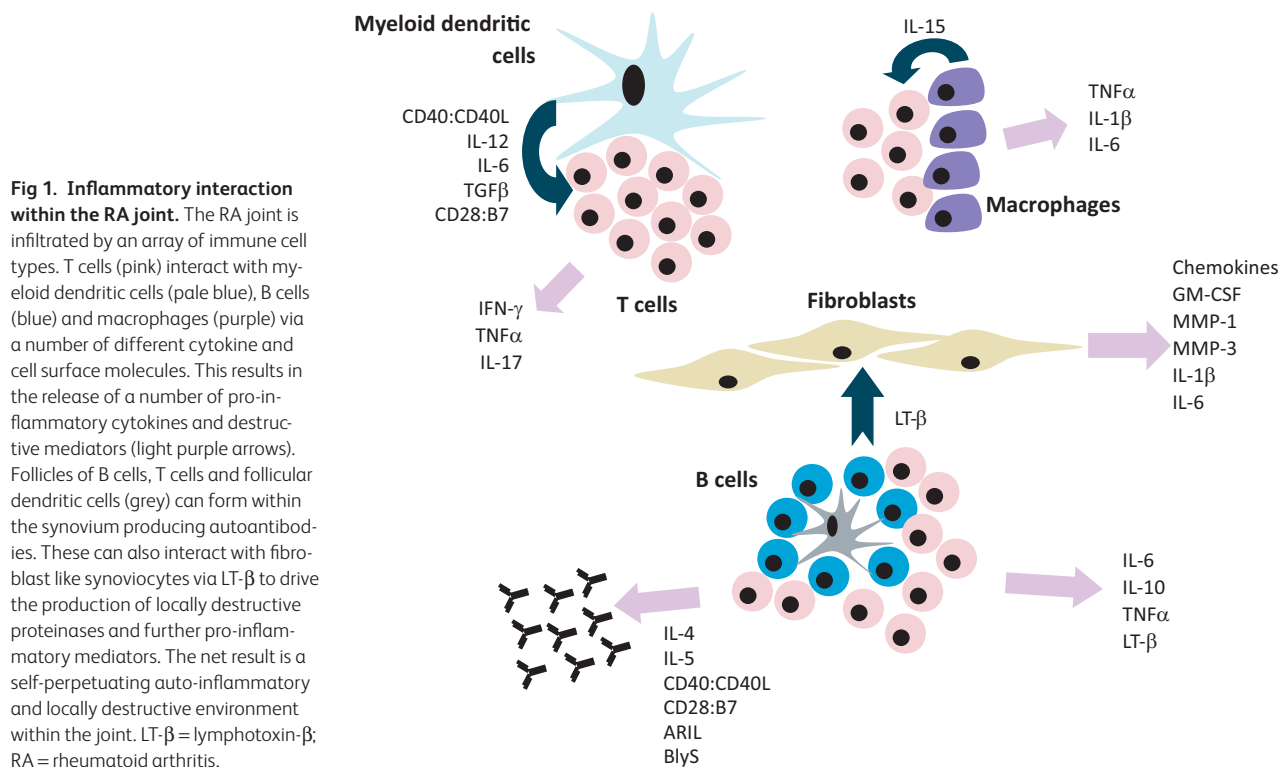The local and systemic fallout from the inflammatory process drives the excess morbidity and mortality in RA patients. At the local joint level two factors lead to disability. In early disease the process of inflammation causes thickening of the synovium and exudation of fluid into the joint. This 'synovitis' results in the characteristic pain, swelling and stiffness in the joints, reducing mobility and level of function. Left unchecked this synovitis underpins joint damage and destruction, which becomes evident in serial radiographs as joint space narrowing and erosions.[2] This bony joint damage correlates with the development of longer-term disability in RA.

Beyond the joint, RA has multiple effects on other organ systems. RA patients have an excess cardiovascular risk that is equivalent to that of diabetes. They have double the risk of having a myocardial infarction and a 70% increased risk of stroke, compared with non-RA matched controls. RA patients have an increased propensity towards infection, even without the addition of immunomodulatory therapies. They also have a markedly increased risk of haematological malignancies: their risk of lymphoma is up to 26 times higher than the general population. Cardiovascular disease and haematological malignancy, in particular, are driven by the cumulative inflammatory load and, consequently, are more common in those who are disabled by the disease. Taken together, poor disease control in RA results in cumulative disability and poor quality of life but also in premature mortality. Indeed, even functional capacity in the first year of disease has been shown to be a predictor of life expectancy.[3]

Improved understanding of the disease and the advent of new therapeutic agents over the last 20 years has proven critical to improving patient outcomes, as discussed in the sections below.

The window of opportunity

The recognition of the paradigm that 'inflammation begets damage begets disability begets mortality' in RA led to the development of aggressive early treatment, and the development of early arthritis clinics. Prior to the 1990s, the management model was the so called 'pyramid' approach. Treatment started with non-steroidal anti-inflammatory drugs and disease modifying therapies (DMARDs), such as penicillamine and gold, were held in reserve for patients with radiographic damage. Glucocorticoids were added when those drugs failed to work, which was a frequent occurrence, and patients became rapidly disabled with cumulative

Fig 1. Inflammatory interaction within the RA joint. The RA joint is infiltrated by an array of immune cell types. T cells (pink) interact with myeloid dendritic cells (pale blue), B cells (blue) and macrophages (purple) via a number of different cytokine and cell surface molecules. This results in the release of a number of pro-inflammatory cytokines and destructive mediators (light purple arrows). Follicles of B cells, T cells and follicular dendritic cells (grey) can form within the synovium producing autoantibodies. These can also interact with fibroblast like synoviocytes via LT-β to drive the production of locally destructive proteinases and further pro-inflammatory mediators. The net result is a self-perpetuating auto-inflammatory and locally destructive environment within the joint. LT-β = lymphotoxin-β; RA = rheumatoid arthritis.

glucocorticoid side effects. With the advent of early arthritis clinics it became apparent that the longer the interval from diagnosis to starting treatment with a DMARD, the poorer the outcome.[4] This was in part due to the accrual of irreversible joint damage, but it also became apparent that the disease could take on a more aggressive phenotype and damage the joints more rapidly regardless of treatment, if not treated sufficiently early. This became known as the 'window of opportunity' and it is now generally accepted that the earlier a patient with RA is diagnosed and started on a disease modifying therapy, the better their long term prognosis (Fig 2). This is true not only for disability outcomes, but also for subsequent probability of drug free disease remission and mortality.
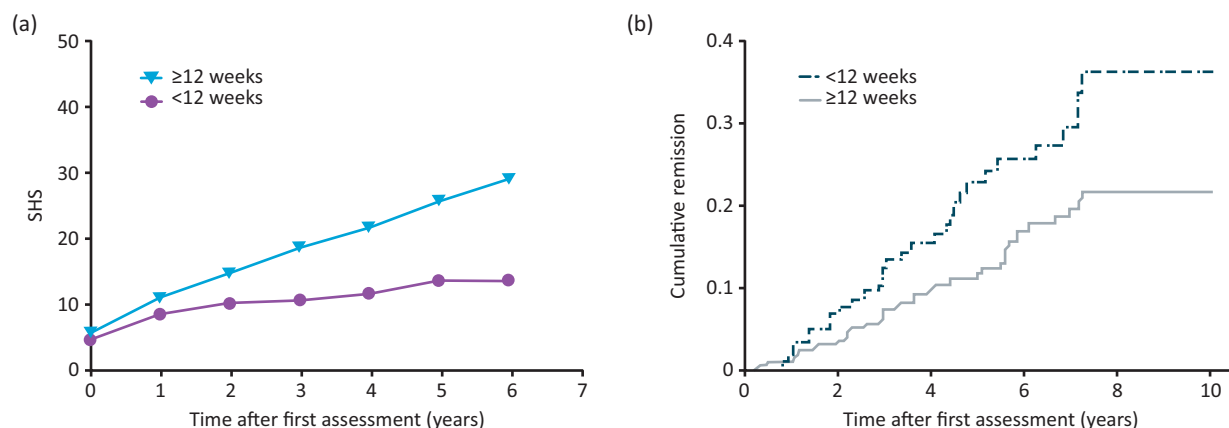
Fig 2. Outcomes in RA following delay in initiation of disease-modifying drugs. (a) demonstrates an enhanced progression of radiographic joint damage if initial assessment was delayed ≥ 12 weeks vs < 12 weeks (n=598). (b) shows the effect of the delay on the probability of achieving DMARD-free disease remission. The delay was the interval from symptom onset to being seen by a rheumatologist. Adapted with permission from Linden *et al.*[4] RA = rheumatoid arthritis; SHS = Sharp Van der Heijde score.

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Treating to target

Having established the benefit of early treatment, the next question was how aggressively to treat these therapies. A further major advancement in RA management was the identification of ways objectively to measure and record ongoing disease activity, using tools such as the Disease Activity Score (DAS). The TICORA study explored the outcomes of patients aggressively treated to a specific disease activity target, in this case maintenance of a low disease activity score.[5] Patients in the treat-to-target group received more intensive therapy and had lower disease activity at 18 months, compared with standard practice (DAS remission 65% vs 16% p<0.0001). The treat-to-target group also had less joint damage progression over the 18 months of follow-up. This treat to a target strategy is analogous to that used widely in other conditions such as diabetes and hypertension. With early institution and escalation of DMARD therapy, approximately 30% of patients will achieve remission. In up to half of these, DMARDs can subsequently be withdrawn without subsequent flare in disease activity (drug-free remission). Typical regimes start with methotrexate with rapid escalation to combination therapy, incorporating sulphasalazine and hydoxychloroquine, with leflunomide a further option. Many guidelines recommend the use of low-dose and intra-articular glucocorticoids to suppress inflammation rapidly while waiting for the DMARDs to exert their effect.[6]

Biologics

Early treatment and treat to target have had major impacts on RA outcomes but a significant proportion of RA patients require more than disease-modifying therapies to bring their disease under control. It is in these patients that biologic therapies (sometimes referred to as biological DMARDs) have had the greatest impact. Biologic therapies are monoclonal antibodies or soluble receptors that target specific aspects of disease pathogenesis. A major attribute of these therapeutics is their ability to rapidly and completely arrest joint damage, which is not always the case with conventional DMARDs, even when used early in disease. The current agents target four key processes or mediators: TNF, B cells, T-cell co-stimulation and IL6.

Anti-TNF

TNF is a key mediator of inflammation in RA and is derived principally from macrophages and T cells. In the late 1990s anti-TNF therapies were trialled in patients with RA. This was the culmination of many years of experimentation studying cytokine cascades in RA synovial tissue and TNF blockade in pre-clinical animal models of RA.[7] These trials clearly demonstrated that, even after failure of the 'conventional' DMARDs, anti-TNF therapies provided not only symptomatic relief but also arrested radiographic joint damage.[8–10] Their use was consequently associated with reduced disability, retained employment and fewer joint operations.[11–13] Five different anti-TNF agents are now licensed for clinical use – etanercept (a fusion protein between the p75 TNF receptor extracellular domain and human IgG1 Fc), infliximab (mouse-human chimeric mAb), adalimumab (fully human mAb), golimumab (fully human mAb) and certolizumab pegol (humanised Fab fragment conjugated to polyethylene glycol).[14] The response rate to TNF blockade varies depending on the stage of disease. In the UK it can be used following the failure of at least two conventional DMARDs and in this setting around 20–30% of patients achieve a good response (ACR70, approximately 70% improvement in disease activity), 40–50% achieve a moderate response (ACR50, approximately) and 60–70% a modest response (ACR20); 30–40% do not respond at all.

While causing less 'global' immune suppression than conventional DMARDs, anti-TNF therapies are highly focused immune modulators with an important spectrum of adverse effects. Compared with 'conventional' DMARDs there is about a 20% increase in risk of serious infection, including opportunistic infection.[15] This risk is maximal in the first 6 months of therapy but then declines. Post-marketing surveillance identified an association between anti-TNF and re-activation of TB.[16] Cases, including disseminated and miliary TB, were identified in 70/147,000 patients on infliximab, suggesting a non-redundant role of TNF in the maintenance of granulomata. Such cases are now effectively prevented by baseline screening for latent TB and appropriate anti-microbial prophylaxis. Pooled analysis of trials has identified no cumulative increased risk of malignancy with anti-TNF, however malignant melanoma may prove to be an exception.[17] Other adverse effects associated with TNF blockade include demyelination, congestive heart failure and rare cases of blood dyscrasias and vasculitis, including drug-induced SLE.

B-cell depletion

B cells are implicated in the pathogenesis of RA and are enriched in the inflammatory pannus of the RA joint. They have a clear role in the generation of auto-reactive antibodies (rheumatoid factor; anti-citrullinated peptide antibodies (ACPA)) and also synthesise pro-inflammatory cytokines (IL6, TNF, lymphotoxin β). They also play a role in the activation of T cells. Rituximab is a chimeric mouse-human mAb against CD20 and acts to deplete the B-cell population while leaving precursor and plasma cell populations intact. It is given as a course of paired infusions which can be repeated after 6 months or more, using a treat-to-target strategy if effective. Rituximab is currently licensed for the treatment of RA following failure of TNF blockade. In this patient population approximately 10–15% achieve a good (ACR70) response.[18]

The risk of serious infection is similar to anti-TNF (approximately 4 per 100 patient years). This risk appears stable across repeated courses of rituximab with no apparent effect of cumulative exposure.[19] Of some concern with rituximab is the very small risk of progressive multifocal leukoencephalopathy, a serious neurodegenerative condition caused by JC virus. The prevalence in RA patients receiving rituximab is approximately 1 per 20,000 patients treated.[20] Other opportunistic infections, however, appear less common than with TNF blockade. The most common adverse reactions associated with rituximab are infusion reactions, which are particularly common at the start of therapy and are a consequence of B-cell lysis. Their incidence and severity can be reduced by the use of prophylactic methylprednisolone infusions.[21]

Co-stimulation blockade

T cells are considered key drivers in the pathogenesis of RA, and their full activation comprises two major events. Binding of the

Fig 3. T-Lymphocyte co-simulation and blockade with abatacept. (a) In physiological conditions the co-stimulation of T lymphocytes upregulates the expression of CTLA-4 which competes with CD28 to limit co-stimulation. (b) Abatacept is a soluble form of the extracellular domain of CTLA-4 and acts to limit activation of T lymphocytes. APC = antigen-presenting cell; CTLA-4 = cytotoxic T-lymphocyte associated antigen 4; MHC = major histocompatibility complex; TCR = T cell receptor.
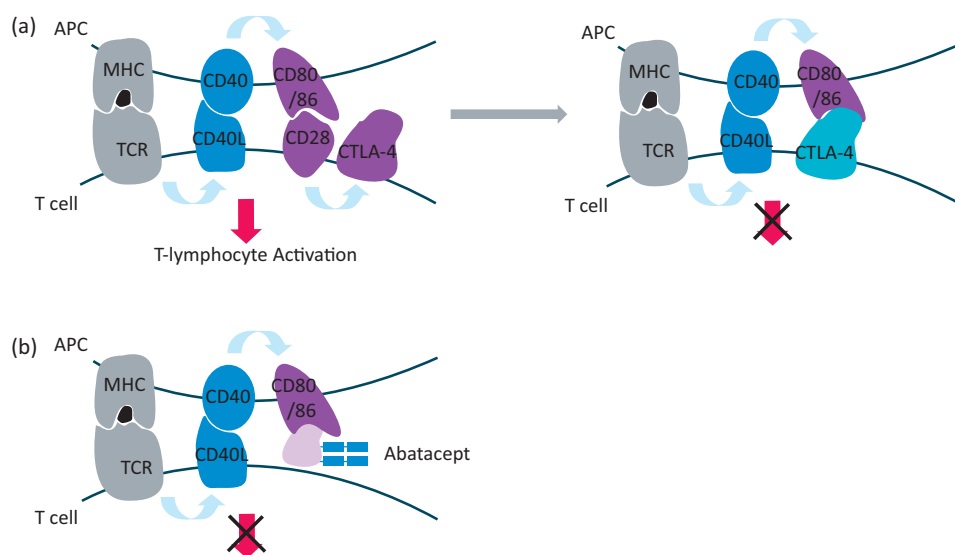
T-cell receptor to the antigen/MHC complex is the initial trigger which then drives a co-stimulation pathway between CD28 on the T cell and CD80 and CD86 on the antigen presenting cell. This pathway triggers full T-cell activation and, subsequently, a negative feedback loop to dampen activation again. This involves upregulation of cell surface cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) which competes with higher affinity than CD28 for binding to CD80 and CD86. This endogenous control system has been harnessed therapeutically by the drug abatacept, which comprises the extracellular domain of CTLA-4 fused to the Fc of human IgG1 (Fig 3).

In the treatment of RA, abatacept can be used following the failure of conventional DMARDs or TNF blockade.[22,23] As expected, the response rate is higher if the drug is administered earlier in disease with similar rates to TNF blockade and rituximab at the same disease stage.[24] As with the other biologic drugs, abatacept is associated with an increased risk of serious infections but no increased risk of malignancy.[25,26] Abatacept can be administered by either iv infusion or subcutaneous injection.

IL6 antagonism

A more recent cytokine target is IL6. IL6 has a variety of roles in inflammation, including driving the proliferation and activity of T cells and B cells. In the synovium it drives fibroblast proliferation and neovascularisation, leading to pannus formation. It is also involved in macrophage and osteoclast maturation as well as driving the acute phase response from hepatocytes. It is an important mediator of the anaemia of chronic disease by interfering with the delivery of iron from the reticuloendothelial system. IL6 also contributes to fatigue, fever, hypo-albuminaemia and hypergammaglobulinaemia and is likely to play a role in the predisposition to cardiovascular disease.

Therapeutically, targeting the IL6 receptor with the humanised mAb tocilizumab provides similar efficacy to the aforementioned biologic drugs. Like abatacept, it can be used either as a first biologic drug or following anti-TNF failure.[27,28] It may provide a particular advantage in patients with anaemia of chronic disease associated with RA.[29] Tocilizumab has a similar risk of serious infection to the other biologics but also carries a small risk of GI perforation.[30]

Future treatments

Over the last 20 years the treatment of RA has advanced to the point that disease control and prevention of disability is not only possible but should be the expected outcome for many patients. However, our ability to stratify patients at presentation with regard to prognosis, and likely treatment response, remains dismal. For example, only around a third of patients respond optimally to methotrexate, and if we could identify likely non-responders then we could choose an alternative DMARD in those patients, potentially avoiding a critical period of poor disease control. In this way the identification of treatment response biomarkers should allow therapy to be individualised and geared towards rapid achievement of drug-free remission. Eventually, the ideal may become prevention of RA by targeting at risk 'pre-rheumatoid arthritis' individuals.

Biomarkers

The discovery of ACPA, which are highly specific for RA, has aided early diagnosis in a proportion of patients (seropositive RA). The third of patients who make neither ACPA nor rheumatoid factor (which is in any case less specific) present a diagnostic difficulty. In terms of prognosis, there are associations between ACPA, C-reactive protein, HLA type and gender with disease severity, but these are not sufficiently robust to guide treatment decisions.

Similarly there is no reliable way to predict therapeutic response. Therefore we are reliant on successive trials of treatment which, in non-responders, may lead to a prolonged period of uncontrolled inflammation. There are two contrasting approaches to this problem. The ideal would be the identification of specific therapeutic biomarkers with which
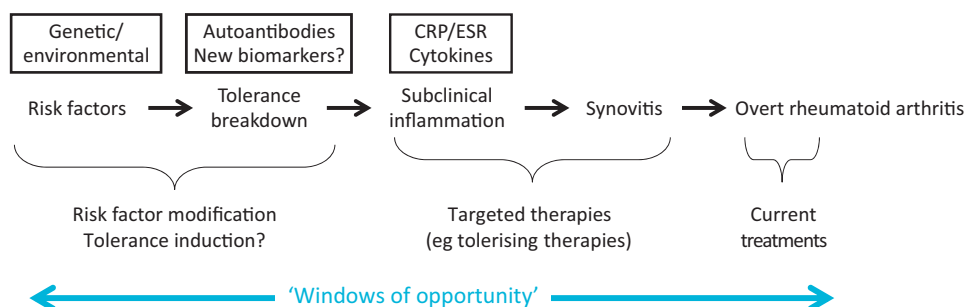
Fig 4. 'Windows of opportunity' to intervene in RA. An understanding of the pathogenesis of RA and biomarkers to identify 'Pre-RA' patients may offer new avenues to intervene at an earlier stage in RA. More targeted therapies may be possible prior to the development of clinical RA. Biomarkers to identify the breakdown of tolerance may allow risk factor modification or tolerising measures to be taken at this point, long before joint damage occurs. Adapted with permission from Isaacs.[31] CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis.

to tailor therapy to the patient, as seen increasingly in other areas of medicine (see above). The alternative approach may be a step down multidrug treatment algorithm, including early biologics. This would give patients early access to the treatments most able to retard joint damage and induce remission. The detractors of this model are the considerably greater upfront costs, plus the knowledge that approximately 30% of patients achieve remission and avoid joint damage on conventional DMARDs alone. This strategy would therefore expose them unnecessarily to the more significant side effect profile of the biologics.[1]

Therapeutic tolerance

The ideal therapy for RA would be to return to a state of immune tolerance in which the autoimmune process is switched off. Operationally this may be the same as drug-free remission, although again the lack of relevant biomarkers renders any distinction impossible to ascertain at present. If such biomarkers could be identified, however, it may become possible to taper therapy of patients in clinical remission that demonstrate the appropriate tolerance 'signature'. This could facilitate a step down approach to RA therapy, allowing aggressive early therapy to either be tapered and stopped in tolerant individuals or switched to a maintenance therapy in others. Tolerance biomarkers would also be necessary to allow the development of a new generation of specific tolerising therapies.[31]

Treating 'pre-rheumatoid arthritis'

The current treatment paradigm for RA involves identifying patients as early as possible after symptom onset and then initiating treatment. However, there is now incontrovertible evidence that this clinical phase of the disease is preceded by a cascade of events that starts with loss of self-tolerance and progresses through a phase of subclinical inflammation. This process may take over 10 years, with autoantibodies being present in serum many years before symptomatic disease.[32] This phase of 'pre-RA' could provide the ideal setting in which to use potentially tolerising treatments, provided such treatments were shown to have a favourable risk to benefit profile[31] (Fig 4). In this way it may be possible to prevent the development of clinical RA, which would greatly reduce the disease burden

on the individual and on society. Lifestyle advice may also play an important role at this stage of the disease, such as smoking cessation and adhering to a healthy diet.

Conclusions

RA has moved from a relentlessly disabling and quality of life limiting disease to a manageable long term condition over the past 20 years. The key to this success have been early and aggressive treatment of inflammation, and new biological treatments when required. To further improve outcomes for RA patients, new biomarkers are needed to track progression of the disease, to predict response to the different therapies, and to identify true immunological remission/tolerance. The future of RA may lie in the re-introduction of immune tolerance rather than controlling ongoing inflammation, potentially removing the need for chronic treatment. ■

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