RHEUMATOLOGY

Rheumatology 2012;51:v3–v11
doi:10.1093/rheumatology/kes113

Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis

Ernest Choy[1]

Abstract

RA is a progressive inflammatory autoimmune disease with articular and systemic effects. Its exact cause is unknown, but genetic and environmental factors are contributory. T cells, B cells and the orchestrated interaction of pro-inflammatory cytokines play key roles in the pathophysiology of RA. Differentiation of naïve T cells into Th 17 (T_H17) cells results in the production of IL-17, a potent cytokine that promotes synovitis. B cells further the pathogenic process through antigen presentation and autoantibody and cytokine production. Joint damage begins at the synovial membrane, where the influx and/or local activation of mononuclear cells and the formation of new blood vessels cause synovitis. Pannus, the osteoclast-rich portion of the synovial membrane, destroys bone, whereas enzymes secreted by synoviocytes and chondrocytes degrade cartilage. Antigen-activated $CD4^+$ T cells amplify the immune response by stimulating other mononuclear cells, synovial fibroblasts, chondrocytes and osteoclasts. The release of cytokines, especially TNF-α, IL-6 and IL-1, causes synovial inflammation. In addition to their articular effects, pro-inflammatory cytokines promote the development of systemic effects, including production of acute-phase proteins (such as CRP), anaemia of chronic disease, cardiovascular disease and osteoporosis and affect the hypothalamic–pituitary–adrenal axis, resulting in fatigue and depression.

Key words: B cell, cytokine, interleukin-1, interleukin-6, interleukin-17, pathogenesis, pathophysiology, rheumatoid arthritis, T cell, tumour necrosis factor-α.

Introduction

RA is a chronic, progressive, inflammatory autoimmune disease associated with articular, extra-articular and systemic effects. It has been reported that RA affects ~0.5–1% of the adult population of developed regions [1–8]. Although some patients have mild self-limited disease, many experience joint destruction, severe physical disability and multiple co-morbidities [9]. Mortality rates are more than twice as high in patients with RA as in the general population [10, 11], and this gap appears to be widening [11].

T cells, B cells and the orchestrated interaction of pro-inflammatory cytokines play key roles in the pathophysiology of RA [12, 13]. The cytokines most directly implicated in this process are TNF-α and IL-6; IL-1 and IL-17 may also play important, albeit arguably less so, roles in the disease process [12]. The goal of this review is to summarize the complex pathobiology of RA as currently understood, highlighting the effects of major immune modulators at both articular and systemic levels. In addition, we briefly discuss how the increased understanding of the pathobiology of RA has led to the development of biologic agents that target specific immune mediators and has resulted in new and effective treatments for RA.

Overview of RA pathobiology

Although the exact cause of RA remains unknown [12], recent findings suggest a genetic basis for disease development. More than 80% of patients carry the epitope of the HLA-DRB1*04 cluster [13], and patients expressing two HLA-DRB1*04 alleles are at elevated risk for nodular disease, major organ involvement and surgery related to joint destruction [14]. Single-nucleotide polymorphism genotyping across the MHC has identified additional alleles related to RA risk, including those found on the conserved A1-B8-DR3 (8.1) haplotype and those near the

[1]King's Musculoskeletal Clinical Trials Unit, King's College London, London, UK.

Submitted 1 December 2011; revised version accepted 29 March 2012.

Present address: Department of Rheumatology, Cardiff University School of Medicine, Cardiff, UK.

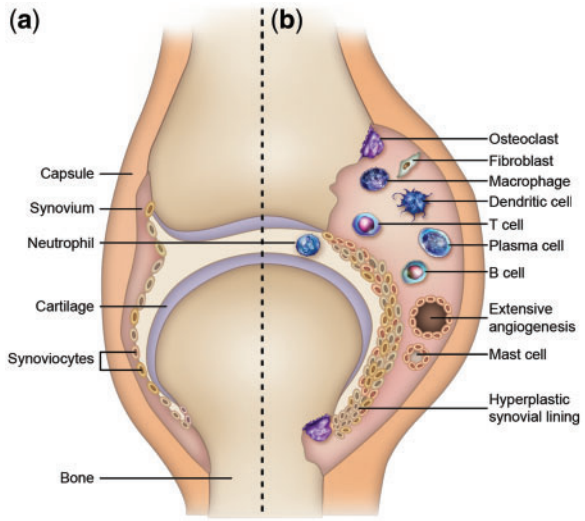
Correspondence to: Ernest Choy, Department of Rheumatology, Cardiff University School of Medicine, 1st Floor, Tenovus Building, Cardiff University Heath Park Campus, Heath Park, Cardiff CF14 4XN, UK. E-mail: choyeh@cardiff.ac.uk

HLA-DPB1 gene [9]. Other RA-associated loci are *PTPN22*, *PADI4*, *STAT4*, *TRAF1-C5* and *TNFAIP3*, although non-MHC risk alleles may represent only 3–5% of the genetic burden of RA [9]. Environmental factors, such as smoking and infection, may also influence the development, rate of progression and severity of RA [15, 16].

Various immune modulators (cytokines and effector cells) and signalling pathways are involved in the pathophysiology of RA [12]. The complex interaction of immune modulators is responsible for the joint damage that begins at the synovial membrane and covers most IA structures (Fig. 1) [12]. Synovitis is caused by the influx or local activation, or both, of mononuclear cells (including T cells, B cells, plasma cells, dendritic cells, macrophages and mast cells) and by angiogenesis [12]. The synovial lining then becomes hyperplastic, and the synovial membrane expands and forms villi [12]. The osteoclast-rich portion of the synovial membrane, or pannus, destroys bone, whereas enzymes secreted by neutrophils, synoviocytes and chondrocytes degrade cartilage [12].

In addition to joint symptoms, many patients experience extra-articular or systemic manifestations, or both [17]. According to a US pharmacy claims data analysis with a mean follow-up of 3.9 years, 47.5% of 16 752 patients with RA experienced at least one extra-articular or systemic manifestation [17]. Extra-articular manifestations include rheumatoid nodules, vasculitis, pericarditis, keratoconjunctivitis sicca, uveitis and rheumatoid lung [17]. Systemic manifestations include acute-phase protein production, anaemia, cardiovascular disease (CVD), osteoporosis, fatigue and depression [18, 19].

Fig. 1 Schematic view of a normal joint (**a**) and a joint affected by RA (**b**) [12].



The joint affected by RA (**b**) shows increased inflammation and cellular activity. Reprinted by permission from Macmillan Publishers Ltd (Nature Reviews Drug Discovery) from [12], © 2003.

Effector cells involved in the pathobiology of RA

The earliest event in RA pathogenesis is activation of the innate immune response, which includes the activation of dendritic cells by exogenous material and autologous antigens (Fig. 2) [12, 13]. Antigen-presenting cells, including dendritic cells, macrophages and activated B cells, present arthritis-associated antigens to T cells. Concurrently, $CD4^+$ T cells that secrete IL-2 and IFN-γ infiltrate the synovial membrane. As noted previously, most patients with RA carry the epitope of the HLA-DRB1*04 cluster [13]. These alleles share a homologous amino acid sequence on the HLA-DR β-chain that confers binding of specific peptides and affects antigen presentation to TCRs [13]. Disease-associated HLA-DR alleles may present arthritis-related peptides, leading to the stimulation and expansion of autoantigen-specific T cells in the joints and lymph nodes [13].

B cells contribute to RA pathogenesis not only through antigen presentation, but also through the production of antibodies, autoantibodies and cytokines (Fig. 2) [13]. RF and anti-CCP autoantibodies are common in patients with RA. B lymphocytes express cell surface proteins, including immunoglobulin and differentiation antigens such as CD20 and CD22 [13]. Autoantibodies can form larger immune complexes that can further stimulate the production of pro-inflammatory cytokines, including TNF-α, through complement and Fc-receptor activation [13].

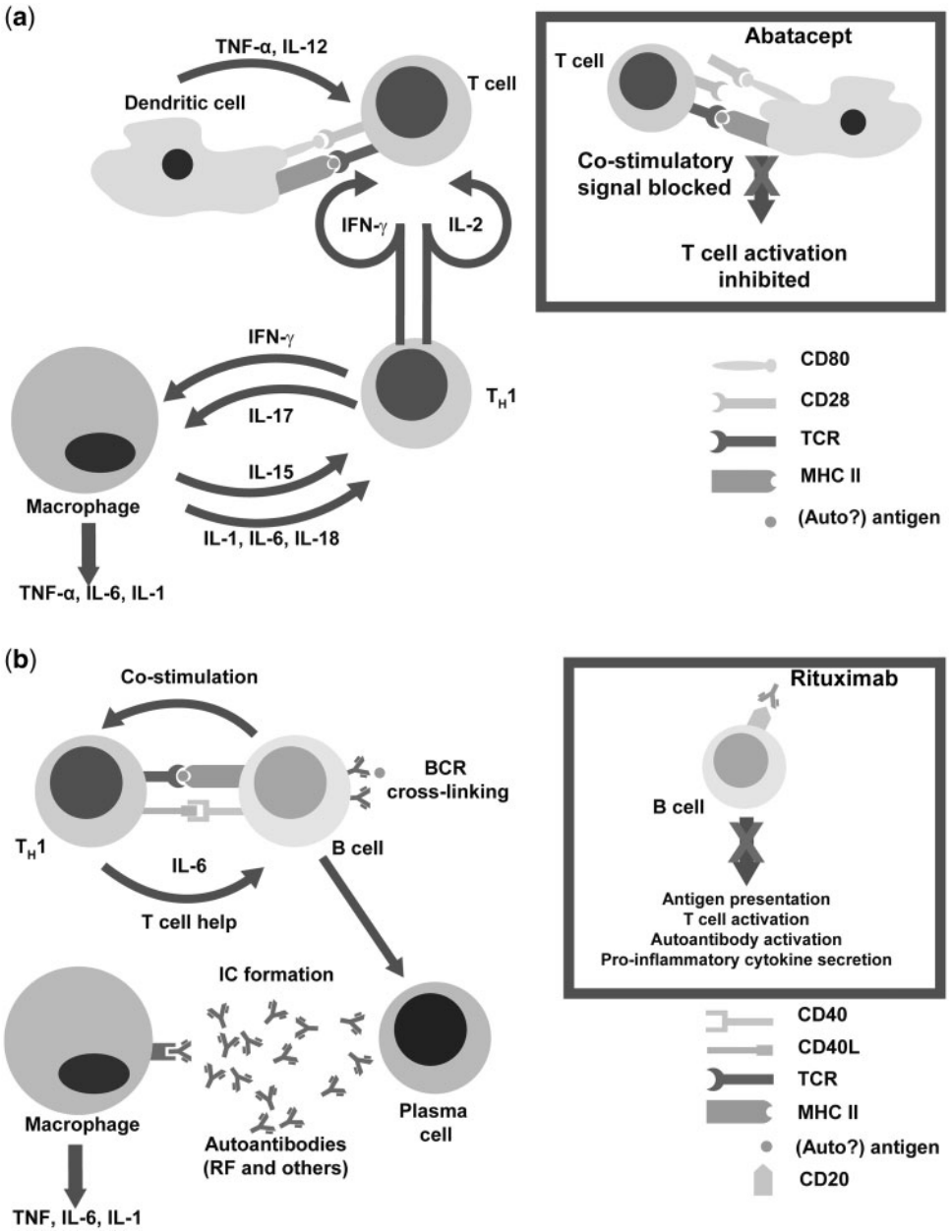
T- and B-cell activation result in increased production of cytokines and chemokines, leading to a feedback loop for additional T-cell, macrophage and B-cell interactions [12, 13]. In addition to antigen presentation, macrophages are involved in osteoclastogenesis and are a major source of cytokines, including TNF-α, IL-1 and IL-6 [12, 13]. Within the synovial membrane there is a great increase in activated fibroblast-like synoviocytes, which also produce inflammatory cytokines, PGs and MMPs [13]. Synoviocytes contribute to the destruction of cartilage and bone by secreting MMPs into the SF and by direct invasion into these tissues [13].

Cytokines and the impact on effector cells

It is well established that pro-inflammatory cytokines (e.g. IL-6 and TNF-α) are involved in the pathogenesis of RA [20, 21]. TNF-α and IL-6 play dominant roles in the pathobiology of RA; however, IL-1, VEGF and perhaps IL-17 also have a significant impact on the disease process. Details on the roles of these cytokines are shown in Table 1 [9, 20, 22–35]. Through complex signal pathways, these cytokines activate genes associated with inflammatory responses, including additional cytokines and MMPs involved in tissue degradation [12]; this is discussed in subsequent sections.

An IL-17-secreting subset of $CD4^+$ cells [i.e. Th 17 (T_H17)] that has a critical role in synovitis has recently been implicated in the pathogenesis of many inflammatory and

FIG. 2 Consequences of the activation of effector cells by cytokines.



(**a**) Effects on T cells. The inset depicts the mechanism of action of abatacept, which inhibits T-cell co-stimulation. (**b**) Effects on B cells. The inset depicts the mechanism of action of rituximab, which selectively depletes $CD20^+$ B cells [12, 13].

autoimmune diseases, including RA [33]. The presence of T_H17 cells in the SF and peripheral blood of patients with RA suggests the involvement of this potent pro-inflammatory cytokine in RA pathology [36, 37]. An *in vivo* study has shown that CIA was markedly suppressed in IL-17-deficient mice [38]. Additionally, the ubiquitous expression of IL-17 receptor (IL-17R) on fibroblasts, endothelial cells, epithelial cells and neutrophils indicates that this cytokine has the potential to influence a number of pathways and effector cells involved in RA [39].

IL-6 signalling

IL-6 is of particular interest because although many cytokines act on target cells close to their site of secretion [40], IL-6 can also exert its effects on distant target cells by way of trans-signalling through ubiquitously

Table 1 Actions of cytokines that play major roles in RA pathobiology

Cytokine	Role in the disease process
TNF-α	Local effects
	Increased monocyte activation, cytokine release, PG release [20]
	Increased polymorphonuclear leucocyte priming, apoptosis and oxidative burst [20]
	T-cell apoptosis, clonal regulation, TCR dysfunction [20]
	Increased endothelial cell adhesion molecule expression, cytokine release [20]
	Decreased synovial fibroblast proliferation, collagen synthesis [20]
	Increased MMP and cytokine release [20]
	Systemic effects
	Acute-phase protein production [22]
	HPA axis dysregulation (fatigue and depression) [24]
	CVD promotion [23]
IL-6	Local effects
	Osteoclast activation [25, 26]
	Neutrophil recruitment [27]
	Pannus formation via promotion of VEGF production [28, 29]
	B-cell proliferation and antibody production [20]
	T-cell proliferation and differentiation [20]
	Systemic effects
	Acute-phase protein production [22]
	Anaemia (via hepcidin production) [30]
	CVD promotion [23]
	Osteoporosis [31, 32]
	HPA axis dysregulation (fatigue and depression) [24]
IL-1	Local effects
	Increased synovial fibroblast cytokine, chemokine, MMP and PG release [20]
	Increased monocyte cytokine, reactive oxygen intermediate and PG release [20]
	Osteoclast activation [20]
	Endothelial cell adhesion molecule expression [20]
	Systemic effects
	Acute-phase protein production [22]
	CVD promotion [23]
	HPA axis dysregulation (fatigue and depression) [24]
IL-17	Recruitment of monocytes and neutrophils by increasing local chemokine production [33]
	Facilitation of T-cell infiltration and activation [33]
	Amplification of immune response (e.g. by induction of IL-6 production) [33]
	Increased synovial fibroblast cytokine and MMP release [20]
	Osteoclastogenesis [20] and cartilage damage [35]
	Synergistic activity with IL-1β, TNF-α and IFN-γ [33, 34]
VEGF	Angiogenesis, contributing to pannus formation [28]

expressed receptors [18]. The classic signalling mechanism is a protein complex that includes a membrane-bound, non-signalling α-receptor unit (IL-6R) and two signal-transducing glycoprotein 130 (gp130) subunits [18]. IL-6 trans-signalling instead involves a soluble receptor (sIL-6R) that lacks transmembrane and cytoplasmic components, is generated either by limited proteolysis of membrane-bound IL-6R or by alternative mRNA splicing and binds to membrane-bound gp130 subunits [18]. As IL-6R is constitutively expressed on relatively few cell types, trans-signalling increases the range of IL-6-responsive cells [18]. For example, endothelial cells and synoviocytes express gp130 but not IL-6R; however, they can respond to IL-6 when sIL-6R is present [18].

IL-6 trans-signalling is a major factor in RA pathogenesis. Studies in sgp130Fc transgenic mice with an IL-6-trans-signalling knockout phenotype demonstrated that recruitment of inflammatory mononuclear cells strictly depended on the IL-6 trans-signalling pathway and that blockade of trans-signalling prevented the development of inflammation [41]. Further, trans-signalling promotes T-cell recruitment by regulating chemokine secretion during inflammation [42]. Trans-signalling also regulates the expression of pre-B-cell colony-enhancing factor, a cytokine-like factor that contributes to B-cell development and plays a significant role in various inflammatory disorders [43]. IL-6 in combination with TGF-β in mice [34] and by different combinations of TGF-β, IL-21, IL-6, IL-23, IL-1β and TNF-α in humans [44–46] is

responsible for the differentiation of naïve T cells into T_H17 cells.

Role of cytokines in RA joint effects

Inflammation

TNF-α, IL-6 and IL-1 are key mediators of cell migration and inflammation in RA [13]. IL-6, in particular, acts directly on neutrophils through membrane-bound IL-6R, which in turn contributes to inflammation and joint destruction by secreting proteolytic enzymes and reactive oxygen intermediates [18]. Furthermore, an *in vitro* study with fibroblasts from patients with RA demonstrates the role of IL-6 in promoting neutrophil recruitment by activated fibroblasts [27]. Although untreated fibroblasts were able to recruit neutrophils, recruitment was inhibited in the presence of anti-IL-6 antibody [27]. The authors concluded that while IL-6 can directly recruit neutrophils, recruitment may also occur indirectly through fibroblasts [27].

Bone and cartilage destruction

Osteoclasts are multinucleated cells formed by the fusion of mononuclear progenitors of the monocyte/macrophage family [47]. The primary mediators of bone destruction, these cells populate the synovial membranes of patients with RA and are polarized on bone [25, 47]. Macrophage-driven osteoclastogenesis requires the presence of macrophage colony-stimulating factor (MCSF) and results from the interaction of the RANK and the RANK ligand (RANKL) [47]. RANKL expression is regulated by pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-17 [25]. MCSF, IL-6 and IL-11 can also support human osteoclast formation from peripheral blood mononuclear cells by a RANKL-independent mechanism [26].

The principal cause of bone erosion is the pannus, which is found at the interface with cartilage and bone [28]. Angiogenesis is a key process in the formation and maintenance of pannus because invasion of cartilage and bone requires increased blood supply [28]. In patients with RA, many pro-angiogenic factors are expressed in the synovium, but VEGF, a potent cytokine, plays the central role in new blood vessel development [28]. VEGF is both a selective endothelial cell mitogen and an inducer of vascular permeability [28, 48]. In cultured synovial fibroblasts from patients with RA, IL-6, in the presence of sIL-6R and in synergy with IL-1β and TNF-α, induces VEGF production [29]. Conversely, anti-IL-6R mAb therapy significantly reduced VEGF concentrations in these cultures, further demonstrating the role of IL-6 in VEGF production [29].

Cartilage degradation in RA occurs when TNF-α, IL-1 and IL-6 activate synoviocytes, resulting in the secretion of MMPs into the SF [12, 13]. Cytokines also activate chondrocytes, leading to the direct release of additional MMPs into the cartilage [12, 13].

Role of cytokines in systemic effects of RA

Acute-phase protein production

The acute-phase response (APR) is the change in the concentration of certain plasma proteins, such as CRP, hepcidin, serum amyloid A, haptoglobin and fibrinogen, following protein synthesis alterations within hepatocytes [18, 22, 49]. IL-6 has the greatest effect on acute-phase protein levels, although IL-1, TNF-α, TGF-β1 and IFN-γ are also contributory [22]. Elevated levels of CRP, a major acute-phase protein, can be detected within 4 h of injury, with peak values usually occurring within 24–72 h [22].

Although an APR generally lasts for only a few days, some components may persist indefinitely [22]. Increased levels of CRP may exacerbate disease-related tissue damage and contribute to the development of further complications, such as CVD [22]. A prospective observational study that evaluated patients within 1 year of their RA diagnosis and then 3 years later found that an elevated baseline CRP level was a significant predictive factor for radiographic damage at the latter evaluation [50]. The relationship between CRP elevation and CVD is discussed later in this review.

Anaemia

After CVD, the most common systemic manifestation of RA is anaemia, which occurs more frequently during the early stage of the disease [17]. In patients with early RA, IL-6 levels are significantly higher in patients with anaemia than in persons without anaemia [51]. Additionally, haemoglobin levels are inversely correlated with IL-6 levels [51]. IL-6 is required for the induction of hepcidin during inflammation and rapidly induces hypoferraemia in humans [30]. Hepcidin, a peptide produced by hepatocytes, is thought to be the principal iron-regulatory hormone and the key mediator of anaemia in patients with chronic disease [49]. Plasma hepcidin inhibits iron release from macrophages in the spleen and iron uptake in the duodenum [49]. *In vivo* data in wild-type mice have shown that after a turpentine-induced inflammatory response, liver hepcidin expression is increased and serum iron is decreased [30]. Conversely, in IL-6 knockout mice, hepcidin levels are reduced, whereas iron levels are slightly increased in response to turpentine treatment [30]. In humans, serum hepcidin levels have been shown to be highest in patients with RA and anaemia, whereas the lowest levels are reported in healthy adults [52].

CVD

The incidence of CVD events in patients with RA is more than three times that in the general population, and this increase is not entirely explained by traditional risk factors [53]. RA is associated with a spectrum of pro-atherogenic changes linked to systemic inflammation [23]. Release of TNF-α, IL-6 and IL-1 from synovial tissue alters the function of distant tissues, including adipose tissue, skeletal muscle, liver and the vascular endothelium [23]. These changes result in insulin resistance, dyslipidaemia,

Table 2 Biologic agents for the treatment of RA

Agent	First approved	Description, mechanism of action
TNF-α inhibitors		
Infliximab [67–69]	August 1998	Binds with high affinity to soluble and membrane-bound TNF-α and inhibits its effect by blocking TNF-α receptor interactions
Etanercept [70, 71]	November 1998	Binds to TNF-α, preventing it from interacting with its receptor
Adalimumab [72, 73]	December 2002	Binds to human TNF-α with high affinity and prevents it from binding to its receptors
Certolizumab [74, 75]	April 2008	Selectively neutralizes membrane-associated and soluble human TNF-α
Golimumab [76]	April 2009	Forms high-affinity, stable complexes with soluble and transmembrane bioactive forms of TNF-α, preventing the binding of TNF-α to its receptors
Other cytokine inhibitors		
Anakinra [77]	November 2001	Neutralizes activity of both IL-1α and IL-1β
Tocilizumab [78]	January 2009	Binds specifically to sIL-6R and mIL-6R; inhibits sIL-6R and mIL-6R-mediated signalling
T- and B-cell inhibitors		
Rituximab [79]	November 1997	B-cell depletion by binding to CD20
Abatacept [80]	December 2005	Inhibits T-cell activation by binding to CD80 and CD86

mIL-6R: membrane-bound IL-6 receptor.

increased global oxidative activity and endothelial dysfunction [23].

RA-related dyslipidaemia is characterized by low total and high-density lipoprotein (HDL) cholesterol, elevated triglyceride and lipoprotein(a) levels and an increase of small, dense low-density lipoprotein (LDL) species [23]. Although the reduction in inflammation in patients with severe RA following treatment with a biologic agent may result in increased levels of total, HDL and LDL cholesterol (and perhaps triglycerides), inflammation reduction decreases CVD risk [54]. Contrary to our understanding of the link between hyperlipidaemia and CVD, the increases in total cholesterol, LDL and triglyceride levels that may follow treatment for severe inflammation should be considered a consequence of inflammation reduction, not a CVD risk factor [54].

IL-6 plasma concentrations are elevated in patients with RA, and the potentially detrimental cardiovascular consequences of these elevations are suggested by the results of a prospective case–control study in 404 healthy men who participated in the Physicians' Health Study [55]. Median IL-6 plasma concentrations at baseline were significantly higher in men who experienced a first myocardial infarction than in those who remained free of CVD during the 6-year follow-up [55]. Furthermore, each quartile increase in the baseline IL-6 concentration was associated with a 38% increase in the risk of future myocardial infarction [55].

Osteoporosis

Osteoporosis is a common systemic manifestation of RA. The increased prevalence observed in this patient population consequently results in an elevated risk of bone fracture [56]. *In vivo* data support a major role for IL-6 in RA-related osteoporosis [31]. IL-6 transgenic mice, which have high circulating levels of IL-6, have osteopaenia, a condition involving accelerated bone resorption caused by increased osteoclastogenesis and reduced bone formation caused by decreased osteoblast activity [31]. However, IL-6-deficient mice with oestrogen deficiency after ovariectomy do not experience an increase in the number of osteoclast precursors or bone loss [32].

Fatigue and depression

Persistent fatigue and high rates of depression are commonly reported in patients with RA [57–61]. Corticotropin-releasing hormone, a key regulator of the hypothalamic–pituitary–adrenal (HPA) axis and the overall stress system, is associated with fatigue, dysthymia, irritability and depression [62, 63]. Case–control studies have demonstrated that the HPA axis is dysregulated to varying degrees in patients with RA [64–66]. HPA axis dysregulation has been reported to be caused in part by the release of various cytokines, including TNF-α, IL-1 and IL-6 [24]. Thus the fatigue and depression frequently observed in persons with RA are primarily mediated by the up-regulation of cytokines known to be associated with its pathology.

Biologic agents for RA therapy: challenges and opportunities

Increased understanding of the pathobiology of RA has led to the development of biologic agents that target various immune mediators involved in the disease process (Table 2) [67–80]. Therapies targeted against TNF-α, IL-1 and IL-6, in addition to T- and B-cell inhibitors, when used alone or in combination with MTX, have resulted in

favourable clinical outcomes in patients with RA [81]. However, although biologic agents are promising, they are not without limitations [82]. For example, the hierarchy of the pathophysiological response is unclear. As many immune mediators work in concert with one another during the disease process, the question becomes what should be targeted first—B cells, T cells or a cytokine. Additionally, it is unclear how the depletion of a subset of lymphocytes (e.g. B cells or T cells) affects RA or the mechanism by which inflammation is actually reduced [81].

Finally, although the favourable efficacy profile of these drugs is promising, there are also several potential clinical challenges, most notably safety, that may be associated with their use (reviewed in the article by Andrea Rubbert-Roth in this supplement [82]). These limitations include, but are not restricted to, systemic immunosuppression resulting in increased infections and reactivation of tuberculosis and increased incidence of lymphomas [83]. Therefore a major goal for the use of biologic agents is to establish that the benefits of these drugs far outweigh any potential adverse events that may be associated with their use in this patient population. Data from published clinical studies coupled with ongoing clinical trials with biologic agents will help address this issue.

Discussion

The pathobiology of RA is multifaceted and involves T cells, B cells and the complex interaction of many pro-inflammatory cytokines, including TNF-α and IL-6. These cytokines are messengers that activate and differentiate effector cells that cause local and systemic symptoms associated with this disease. The numerous immune mediators that contribute to the pathobiology of RA suggest that many cytokine-based therapies may provide favourable clinical outcomes. Ongoing studies are aimed at further elucidating the role of biologic agents for the treatment of patients with RA. Detailed evaluation of biologic agents in clinical trials, as well as in post-marketing surveillance studies, will help to ensure that these drugs are not only effective but also safe for use in this patient population.

Rheumatology key messages

- RA is a progressive disease in which T cells and B cells interact with cytokines.
- Understanding of the pro-inflammatory cascade in RA has permitted the development of targeted biologic agents.
- IL-6 is one of the most abundant cytokines in the SF of RA patients.

Acknowledgements

The author thanks ApotheCom for writing and editorial assistance, which was funded by F. Hoffmann-La Roche Ltd.

Funding: This study was funded by Roche. Support for third-party writing assistance for this supplement was provided by F. Hoffmann-La Roche Ltd.

Supplement: This paper forms part of the supplement 'Current Treatment Options and New Directions in the Management of Rheumatoid Arthritis'. This supplement was commissioned and funded by F. Hoffmann-La Roche Ltd.

Disclosure statement: E.C. has received research grants from and served as a member of advisory boards and speaker bureaus of Abbott Laboratories, Allergan, AstraZeneca, Boehringer Ingelheim, Chelsea Therapeutics, Chugai Pharma, Eli Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Merrimack Pharmaceutical, Merck Sharp & Dohme, Pfizer, Pierre Fabre Medicament, Roche, Schering Plough, Synovate, UCB and Wyeth.

References

1 Cimmino MA, Parisi M, Moggiana G, Mela GS, Accardo S. Prevalence of rheumatoid arthritis in Italy: the Chiavari Study. Ann Rheum Dis 1998;57:315–8.

2 Carbonell J, Cobo T, Balsa A, Descalzo MA, Carmona L. The incidence of rheumatoid arthritis in Spain: results from a nationwide primary care registry. Rheumatology 2008; 47:1088–92.

3 Symmons D, Turner G, Webb R *et al*. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology 2002;41:793–800.

4 Riise T, Jacobsen BK, Gran JT. Incidence and prevalence of rheumatoid arthritis in the county of Troms, northern Norway. J Rheumatol 2000;27:1386–9.

5 Simonsson M, Bergman S, Jacobsson LT, Petersson IF, Svensson B. The prevalence of rheumatoid arthritis in Sweden. Scand J Rheumatol 1999;28:340–3.

6 Saraux A, Guedes C, Allain J *et al*. Prevalence of rheumatoid arthritis and spondyloarthropathy in Brittany, France. Societe de Rhumatologie de l'Ouest. J Rheumatol 1999;26:2622–7.

7 Boyer GS, Benevolenskaya LI, Templin DW *et al*. Prevalence of rheumatoid arthritis in circumpolar native populations. J Rheumatol 1998;25:23–9.

8 Jacobsson LT, Hanson RL, Knowler WC *et al*. Decreasing incidence and prevalence of rheumatoid arthritis in Pima Indians over a twenty-five-year period. Arthritis Rheum 1994;37:1158–65.

9 Plenge RM. Rheumatoid arthritis genetics: 2009 update. Curr Rheumatol Rep 2009;11:351–6.

10 Wolfe F, Mitchell DM, Sibley JT *et al*. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481–94.

11 Gonzalez A, Maradit KH, Crowson CS *et al*. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56:3583–7.

12 Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003;2:473–88.

13 Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet 2007;370:1861–74.

14 Weyand CM, Hicok KC, Conn DL, Goronzy JJ. The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. Ann Intern Med 1992;117:801–6.

15 Klareskog L, Padyukov L, Alfredsson L. Smoking as a trigger for inflammatory rheumatic diseases. Curr Opin Rheumatol 2007;19:49–54.

16 Getts MT, Miller SD. 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: triggering of autoimmune diseases by infections. Clin Exp Immunol 2010;160:15–21.

17 Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. Curr Med Res Opin 2008;24:469–80.

18 Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. Rheumatology 2010; 49:15–24.

19 Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. Clin Exp Rheumatol 2005;23:S43–52.

20 McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 2007;7:429–42.

21 Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356–61.

22 Panichi V, Migliori M, De Pietro S *et al*. The link of biocompatibility to cytokine production. Kidney Int 2000; 58:96–103.

23 Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how 'high-grade' systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003;108: 2957–63.

24 Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995; 332:1351–62.

25 Schett G. Cells of the synovium in rheumatoid arthritis. Osteoclasts. Arthritis Res Ther 2007;9:203.

26 Kudo O, Sabokbar A, Pocock A *et al*. Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. Bone 2003;32:1–7.

27 Lally F, Smith E, Filer A *et al*. A novel mechanism of neutrophil recruitment in a coculture model of the rheumatoid synovium. Arthritis Rheum 2005;52:3460–9.

28 Paleolog EM. Angiogenesis in rheumatoid arthritis. Arthritis Res 2002;4:S81–90.

29 Nakahara H, Song J, Sugimoto M *et al*. Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis. Arthritis Rheum 2003;48:1521–9.

30 Nemeth E, Rivera S, Gabayan V *et al*. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest 2004; 113:1271–6.

31 de Benedetti F, Rucci N, Del Fattore A *et al*. Impaired skeletal development in interleukin-6-transgenic mice: a model for the impact of chronic inflammation on the growing skeletal system. Arthritis Rheum 2006;54: 3551–63.

32 Poli V, Balena R, Fattori E *et al*. Interleukin-6 deficient mice are protected from bone loss caused by estrogen depletion. EMBO J 1994;13:1189–96.

33 Nalbandian A, Crispin JC, Tsokos GC. Interleukin-17 and systemic lupus erythematosus: current concepts. Clin Exp Immunol 2009;157:209–15.

34 Bettelli E, Carrier Y, Gao W *et al*. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006;441:235–8.

35 Koenders MI, Lubberts E, Oppers-Walgreen B *et al*. Induction of cartilage damage by overexpression of T cell interleukin-17A in experimental arthritis in mice deficient in interleukin-1. Arthritis Rheum 2005;52:975–83.

36 Shahrara S, Huang Q, Mandelin AM, Pope RM. TH-17 cells in rheumatoid arthritis. Arthritis Res Ther 2008;10: R93.

37 Yue C, You X, Zhao L *et al*. The effects of adalimumab and methotrexate treatment on peripheral Th17 cells and IL-17/IL-6 secretion in rheumatoid arthritis patients. Rheumatol Int 2010;30:1553–7.

38 Nakae S, Nambu A, Sudo K, Iwakura Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. J Immunol 2003;171:6173–7.

39 Kolls JK, Linden A. Interleukin-17 family members and inflammation. Immunity 2004;21:467–76.

40 Heinrich PC, Behrmann I, Muller-Newen G, Schaper F, Graeve L. Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. Biochem J 1998;334(Pt 2): 297–314.

41 Rabe B, Chalaris A, May U *et al*. Transgenic blockade of interleukin 6 transsignaling abrogates inflammation. Blood 2008;111:1021–8.

42 McLoughlin RM, Jenkins BJ, Grail D *et al*. IL-6 trans-signaling via STAT3 directs T cell infiltration in acute inflammation. Proc Natl Acad Sci USA 2005;102:9589–94.

43 Nowell MA, Richards PJ, Fielding CA *et al*. Regulation of pre-B cell colony-enhancing factor by STAT-3-dependent interleukin-6 trans-signaling: implications in the pathogenesis of rheumatoid arthritis. Arthritis Rheum 2006;54: 2084–95.

44 Yang L, Anderson DE, Baecher-Allan C *et al*. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature 2008;454:350–2.

45 Volpe E, Servant N, Zollinger R *et al*. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat Immunol 2008;9:650–7.

46 Manel N, Unutmaz D, Littman DR. The differentiation of human T(H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgammat. Nat Immunol 2008;9:641–9.

47 Teitelbaum SL. Bone resorption by osteoclasts. Science 2000;289:1504–8.

48 Koch AE. Angiogenesis as a target in rheumatoid arthritis. Ann Rheum Dis 2003;62:ii60–7.

49 Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood 2003;102: 783–8.

50 Combe B, Dougados M, Goupille P *et al*. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis Rheum 2001; 44:1736–43.

51 Nikolaisen C, Figenschau Y, Nossent JC. Anemia in early rheumatoid arthritis is associated with interleukin 6-mediated bone marrow suppression, but has no effect on disease course or mortality. J Rheumatol 2008;35: 380–6.

52 Demirag MD, Haznedaroglu S, Sancak B *et al*. Circulating hepcidin in the crossroads of anemia and inflammation associated with rheumatoid arthritis. Intern Med 2009;48: 421–6.

53 del Rincon I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737–45.

54 Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis 2009;68:460–9.

55 Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767–72.

56 van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:3104–12.

57 Hewlett S, Cockshott Z, Byron M *et al*. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Rheum 2005;53:697–702.

58 Kojima M, Kojima T, Suzuki S *et al*. Depression, inflammation, and pain in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:1018–24.

59 Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407–17.

60 Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol 1995;22: 639–43.

61 Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos GA. Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis Rheum 2004;51:578–85.

62 Chrousos GP. Regulation and dysregulation of the hypothalamic-pituitary-adrenal axis. The corticotropin-releasing hormone perspective. Endocrinol Metab Clin North Am 1992;21:833–58.

63 Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992;267:1244–52.

64 Eijsbouts AM, van den Hoogen FH, Laan RF *et al*. Hypothalamic-pituitary-adrenal axis activity in patients with rheumatoid arthritis. Clin Exp Rheumatol 2005;23: 658–64.

65 Harle P, Straub RH, Wiest R *et al*. Increase of sympathetic outflow measured by neuropeptide Y and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with systemic lupus erythematosus and rheumatoid arthritis: another example of uncoupling of response systems. Ann Rheum Dis 2006;65:51–6.

66 Harbuz MS, Korendowych E, Jessop DS *et al*. Hypothalamo-pituitary-adrenal axis dysregulation in patients with rheumatoid arthritis after the dexamethasone/corticotrophin releasing factor test. J Endocrinol 2003;178:55–60.

67 Remicade® (infliximab) for IV injection [prescribing information]. Malvern, PA, USA: Centocor Ortho Biotech, Inc., 2009.

68 Remicade 100 mg powder for concentrate for solution for infusion [summary of product characteristics]. Leiden, The Netherlands: Centocor B.V., 2009.

69 Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med 2006;355:704–12.

70 Enbrel 25 mg powder and solvent for solution for injection [summary of product characteristics]. Berkshire, UK: Wyeth Europa Ltd, 2010.

71 Enbrel® (etanercept) for subcutaneous injection [prescribing information]. Thousand Oaks, CA, USA: Amgen Inc. and Wyeth Pharmaceuticals, 2009.

72 Humira 40 mg solution for injection [summary of product characteristics]. Berkshire, UK: Abbott Laboratories Ltd, 2010.

73 Humira (adalimumab) injection, solution [prescribing information]. North Chicago, IL, USA: Abbott Laboratories, 2009.

74 Cimzia® 200 mg solution for injection [summary of prescribing information]. Brussels, Belgium: UCB, Inc., 2009.

75 Cimzia® (certolizumab pegol) [prescribing information]. Smyrna, GA, USA: UCB, Inc., 2009.

76 Simponi 50 mg solution for injection in pre-filled pen [summary of product characteristics]. Leiden, The Netherlands: Centocor B.V., 2009.

77 Kineret 100 mg solution for injection [summary of product characteristics]. Stockholm, Sweden: Biovitrum AB, 2009.

78 RoActemra 20 mg/ml concentrate for solution for infusion [summary of product characteristics]. Welwyn Garden City, UK: Roche Registration Ltd, 2009.

79 MabThera 100 mg (10mg/ml) concentrate for solution for infusion [summary of product characteristics]. Welwyn Garden City, UK: Roche Registration Ltd, 2008.

80 Orencia® 250 mg powder for concentrate for solution for infusion [summary of product characteristics]. Uxbridge, UK: Bristol-Meyers Squibb Pharma EEIG, 2009.

81 Scheinecker C, Redlich K, Smolen JS. Cytokines as therapeutic targets: advances and limitations. Immunity 2008;28:440–4.

82 Rubbert-Roth A. Assessing the safety of biologic agents in patients with rheumatoid arthritis. Rheumatology 2012; 51(Suppl 5):38–47.

83 Feely MG, Erickson A, O'Dell JR. Therapeutic options for rheumatoid arthritis. Expert Opin Pharmacother 2009;10: 2095–106.