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in Systemic Sclerosis

METEOR: an IT Tool in RA

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Innovative Approaches in Systemic Sclerosis

Thomas Hügler, MD, Christiaan A Huigens, Vanessa E Hogan PhD, and Jacob M van Laar, MD, PhD

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A PDF of this article is also available free from
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Systemic sclerosis (SSc) is characterized by progressive fibrosis of the skin and internal organs. The chronic and highly heterogenic disease course has substantially hampered research into SSc in the past. However, the advent of new research tools and animal models has permitted a deeper insight into the pathogenesis of SSc. New findings have been described in the fields of genetic and epigenetic research, cytokine expression, pathogenic autoantibodies, and defective blood progenitor and effector cells. As a consequence, new therapeutic compounds are being developed and tested in SSc patients. Drugs that have been successfully used in other diseases are currently being investigated in controlled trials in SSc. In addition to a “targeted” approach, for example inhibiting single cytokines or protein kinases, autologous stem cell transplantation is successfully being used as a broader approach aimed at “resetting” the immune system. This article provides an overview of the most promising advances in the SSc research field, with an emphasis on pathogenic and therapeutic aspects. *Int J Adv Rheumatol* 2009;7(2):35–43.

Systemic sclerosis (SSc) is a chronic connective tissue disease, characterized by vasculopathy, autoimmunity, and fibrosis of the skin and inner organs (**Figure 1**). Raynaud’s syndrome is commonly the first symptom, sometimes preceding other clinical manifestations by many years. SSc is a heterogeneous disease with a spectrum ranging from a limited cutaneous to a diffuse systemic form.

According to a large study conducted in the US, SSc has an incidence of 20 cases per million adults per year [1]. As a result of its rarity, clinical heterogeneity, and chronic, long-standing disease course, clinical research is difficult and the therapeutic compounds available are limited. Notwithstanding these limitations, recent breakthroughs in our understanding of the pathogenetic mechanisms, achieved using new techniques and clinical trials, indicate that we are at the dawn of a new era.

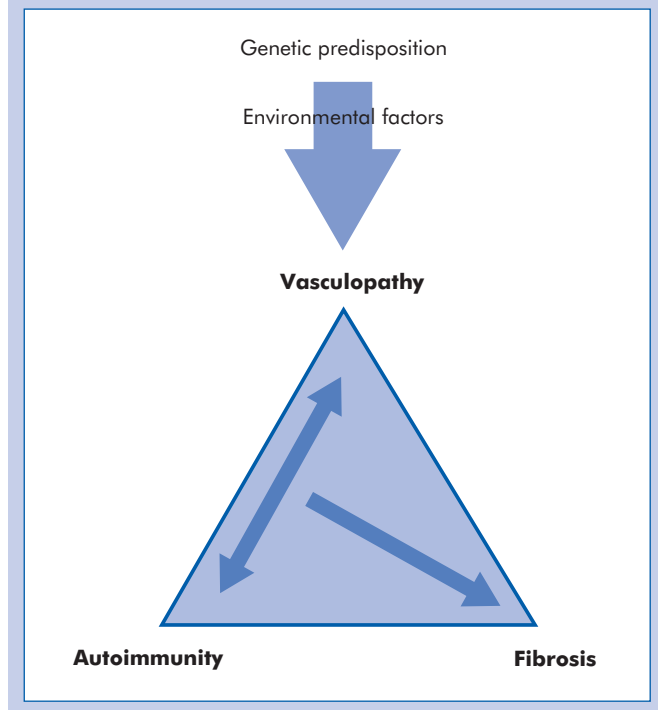
Similar to other autoimmune diseases, a genetic predisposition interacting with environmental factors plays a role in SSc. Gene array analysis has demonstrated a profound and pivotal disturbance of the cytokine environment both in tissue

and in blood. Defects in circulating endothelial progenitor cells on the one hand, and activation of monocytes or other effector cells on the other, have both been described in SSc. Furthermore, a growing range of autoantibodies directed against endothelium, fibroblasts, and other structures have been characterized that may be involved in maintaining the disease process.

This important work on pathogenicity has subsequently led to the development of new therapeutic agents. Therapeutic compounds successfully used in other diseases, mostly of cardiovascular (atherosclerosis), myeloproliferative (chronic myeloid leukemia) or autoimmune (systemic lupus erythematosus [SLE], rheumatoid arthritis [RA]) origin, are also being investigated in SSc. The majority of agents currently under investigation target vasculopathy or autoimmunity. In contrast, the treatment of fibrosis *per se* is still in its infancy but is clearly of great interest. The efficacy of antifibrotic agents has now been observed in animal models such as the bleomycin-induced experimental SSc or “tight skin” (Tsk1/+) mouse model. Demonstration of the reversibility of fibrosis in SSc patients by stem cell transplantation has raised hopes that more targeted antifibrotic compounds can be developed. Stem cell transplantation allows for the complete “resetting” of the

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Figure 1. Pathogenic concepts in systemic sclerosis [79].



immune system, affecting vasculopathy, autoimmunity, and fibrosis. Timing of treatment may be of utmost importance, as some pathogenetic pathways may not be active at all stages of the disease. For example, antifibrotic strategies may be less effective in very early disease when inflammation predominates.

“Systemic sclerosis (SSc) is a chronic connective tissue disease, characterized by vasculopathy, autoimmunity, and fibrosis of the skin and inner organs”

Prospective, randomized, multicenter trials are ongoing and the recent setup of a multicenter online database will permit further insight into prognostic factors and the development of new therapies.

This article presents an overview of selected innovative concepts in the pathogenesis and therapy of SSc.

Pathogenic concepts

Genetic predisposition

The completion of the human genome sequence as well as the advent of efficient and affordable genome-wide association studies (GWAS) have greatly facilitated the discovery and investigation of many new gene mutation candidates (in particular, single nucleotide polymorphisms [SNPs]) in

autoimmune diseases (see <http://genome.gov/gwastudies>). Recently, a polymorphism (G-945C) in the promoter region of the connective-tissue growth factor (*CTGF*) gene was found to be more common in patients with SSc [2]. Furthermore, the protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) gene, which is involved in several autoimmune diseases, seems to contain the mutation 1858C>T. This mutation is associated with a genetic susceptibility to SSc, especially in the subset of patients with anti-topoisomerase 1 (anti-Scl-70) antibodies [3]. Another association with SSc has been described for a SNP within the interleukin-10 receptor gene (*IL-10RB*) and interferon-regulating factor 5 [4,5].

New genetic techniques may also allow the detection of mutations other than SNPs, for example “copy number polymorphisms”, in SSc. In addition, further insights into the pathogenesis of SSc may be gained from epigenetic studies such as DNA methylation, histone modification, imprinting, or gene silencing analyses.

Cytokine environment

Cytokines are key mediators of tissue homeostasis. They have a wide range of effects on cells including effects on growth, interaction, migration, and differentiation, and also stimulate the production and degradation of extracellular matrix (ECM). A major disturbance of the cytokine environment has been described in the tissue and serum of SSc patients. In fact, this disequilibrium is believed to be one of the main causes of the disease [6]. Both pro- and anti-inflammatory cytokines are increased in the serum and affected tissue of patients (**Table 1**) [7]. A shift in T helper (Th) cell polarization towards Th2 cells is commonly observed, which reverses in cases of regression of the disease [8].

IL-4 and -10 are profibrotic cytokines that are typically associated with Th2-polarized cells. Both are upregulated in SSc serum and have been shown to stimulate the expression of collagen in fibroblasts and the differentiation of monocytes into fibrocytes or myofibroblasts. Transforming growth factor- β (TGF- β) is one of the most potent profibrotic cytokines, and plays a key role in SSc pathogenesis. TGF- β stimulates collagen expression by fibroblasts via the SMAD transcription factor pathway and mediates the differentiation of monocytes into myofibroblasts. In SSc tissue, TGF- β is mainly expressed perivascularly within mononuclear infiltrates [9]. In contrast to findings in tissue, SSc patients have reduced serum levels of TGF- β [10]. IL-6 is a pro-inflammatory cytokine that is elevated in SSc sera and correlates with disease severity. Fibroblasts of SSc patients produce more IL-6 compared with fibroblasts from healthy individuals. Monocyte chemoattractant protein-1 (MCP-1; also known as CCL2) is a chemotactic protein that recruits monocytes, memory T cells, and dendritic cells to the site of inflammation. Elevated MCP-1 levels have been described in the early stage of SSc and correlate with

Table 1. Cytokines and chemokines involved in systemic sclerosis.		
Cytokine	Characteristic	Significance in SSc
TGF- β	Profibrotic	Elevated in tissue, reduced in serum, ECM upregulation
IL-6	Inflammatory	Elevated in serum
IL-4, IL-10	Profibrotic	Increased collagen production, myofibroblast differentiation
PDGF	Profibrotic	Stimulation of PDGF receptor by autoantibodies
MCP-1	Chemoattractant	Elevated in tissue, correlation with disease activity
TNF- α	Inflammatory	Increased in serum and tissue, upregulation of TACE in monocytes, inhibition of collagen production in fibroblasts
Type 1 IFN	Autoimmunity trigger, differentiation factor	Elevated in tissue, monocyte activation
ECM: extracellular matrix; IFN: interferon; IL: interleukin; MCP-1: monocyte chemoattractant protein-1; PDGF: platelet-derived growth factor; TNF- α : tumor necrosis factor- α ; TACE: TNF- α -converting enzyme; TGF- β : transforming growth factor- β .		

anti-topoisomerase or anti-RNA polymerase I/III antibody reactivity, and with organ-based complications [11]. Tumor necrosis factor- α (TNF- α) has been shown to be an important cytokine in SSc, although its exact role remains controversial. TNF receptors are overexpressed in SSc skin [12]. Both TNF- α and soluble TNF receptor levels are higher in the sera of SSc patients; furthermore, the latter correlates with inflammation and disease progression. Interestingly, upregulation of TNF- α -converting enzyme (TACE), which sheds the receptor from the cell surface, has been described in peripheral monocytes from SSc patients [13]. Functional data on TNF- α in SSc demonstrate that it inhibits collagen expression in fibroblasts [14], presumably by downregulation of TGF- β receptor 2 [15]. Conversely, TNF- α has profibrogenic properties manifested in the inhibition of phagocytosis of collagen by fibroblasts [16] and stimulation of collagen expression in intestinal myofibroblasts [17]. The net effect of TNF- α in SSc remains unclear.

“TGF- β plays a key role in SSc pathogenesis”

Type 1 interferons (IFNs), including IFN- α and - β , have recently been shown to be involved in SSc pathogenesis. Known as a mainstay of antiviral host defense, type 1 IFNs are also of importance in several autoimmune diseases, in particular SLE. Possible mechanisms by which IFNs contribute to autoimmunity include hypergammaglobulinemia, increased antigen presentation, and the induction of autoantibodies. Case series have been reported describing the occurrence of

SSc during or after treatment with IFN- α or - β in patients with hepatitis C, multiple sclerosis, and myelodysplastic syndrome [18]. Remission or stabilization of SSc symptoms has been described after cessation of IFN treatment. In a previous clinical trial using IFN- α as a possible treatment for SSc, deleterious effects were described in terms of lung fibrosis [19]. Increased levels of IFN are found perivascularly in the skin and serum of SSc patients [20]. Compared with monocytes from healthy controls, monocytes from patients with SSc have been found to express significantly increased levels of IFN-regulated genes such as *Siglec-1* (CD169), described as an IFN fingerprint [21]. Incubation of peripheral blood mononuclear cells (PBMCs) from healthy controls with sera from SSc patients (containing anti-topoisomerase I autoantibodies) has been found to lead to overexpression of type 1 IFN [22].

Vascular dysfunction

The clinical observation of Raynaud’s phenomenon as the first clinical sign, and the perivascular mononuclear infiltrate observed in the early phase of SSc, suggest that endothelial involvement is one of the initial pathogenic steps in SSc [23]. In this context, capillaroscopy has evolved as an important diagnostic tool in SSc, especially in early disease [24]. Pathological studies have described an early, destructive vasculopathy mainly affecting the capillaries, followed by a late, proliferative vasculopathy of small arteries.

A recently described concept is cross-reactivity of antiviral (e.g. cytomegalovirus [CMV]) antibodies with endothelial structures. Molecular mimicry in which antibodies recognize both the human CMV late protein UL94 and the integrin–novel antigen-2 (NAG-2) complex can lead to apoptosis of endothelial cells [25]. Another possible pathogenic mechanism of vasculopathy is an insufficient supply of functional endothelial precursor cells (EPC). Reduced numbers and functional impairment of EPC have been described in the bone marrow of SSc patients [26]. In fact, incubation of healthy EPC with serum from SSc patients leads to apoptosis, suggesting that SSc sera contains apoptosis-inducing factors [27]. Another study showed an impairment of endothelial cell differentiation from bone marrow-derived mesenchymal stem cells (MSCs) [28].

Endothelin-1 (ET-1), a peptide secreted by endothelial cells, has also been shown to be elevated in SSc. Its production leads to constriction of the underlying smooth muscle cells. ET-1 stimulates fibroblasts to produce and contract ECM. Blockade of ET-1 leads to a reduction of type 1 collagen and α -smooth muscle actin by these cells [29].

Autoimmunity

A humoral response in the form of autoantibodies is currently the best marker for autoimmunity in SSc. A T cell proliferative response to type 1 collagen has been reported in 32% of patients with SSc in one study [30]. The autoantibodies that are

Table 2. Autoantibodies in systemic sclerosis.		
Autoantibody	Target	Pathogenicity
ACA	Centromeres	Not known
Scl-70	Topoisomerase	Not known
Anti-endothelial	NAG-2	Apoptosis, ECM expression
Anti-fibroblast	Fibrillin-1	ECM expression via TGF- β pathway
	NAG-2	Fibroblast activation/ECM expression
Anti-MMP	MMP-1 and -3	Inhibition of ECM degradation
Anti-PDGF	PDGF receptor	Collagen expression, production of reactive oxygen species
ACA: anti-centromere antibodies; ECM: extracellular matrix; MMP: matrix metalloproteinase; PDGF: platelet-derived growth factor; NAG-2: novel antigen-2; TGF- β : transforming growth factor- β .		

classically associated with SSc are anti-centromere antibodies and anti-topoisomerase I (anti-Scl-70). In contrast to SLE, no pathogenic role has been attributed to autoantibodies in SSc thus far, and B cells have long been believed to be mere bystanders in SSc. However, it seems that the role of B cells and autoantibody production has been underestimated. As measured by DNA microarrays, B cell genes in clinically affected skin from SSc patients are upregulated [31]. Furthermore, B cells found in SSc skin are characterized by an expanded naïve B cell population and by an activated memory B cell subset. Increased serum levels of BAFF (B-cell activating factor), a potent B cell survival factor, have been detected and positively correlate with the severity of skin fibrosis. Within the last few years, several new autoantibodies with a pathogenic role in SSc have been discovered (Table 2).

“Autoantibodies that are classically associated with SSc are anti-centromere antibodies and anti-topoisomerase I (anti-Scl-70)”

Anti-endothelial cell antibodies have been shown to induce apoptosis in human dermal microvascular endothelial cells [32]. As mentioned above, anti-endothelial antibodies that are directed against the surface integrin–NAG-2 protein complex also recognize the human CMV late protein UL94, suggesting molecular mimicry [25]. A stimulatory effect of anti-NAG-2 antibodies on fibroblasts, resulting in upregulation of ECM expression, has been described [33]. Anti-fibroblast antibodies directed against the protein fibrillin-1 have been detected in a significant proportion of patients with scleroderma. They are capable of activating fibroblasts *in vitro* via the TGF- β pathway,

resulting in increased ECM production [34]. The induction of profibrotic chemokines by anti-fibroblast antibodies seems to be toll like receptor-4-dependent [35]. Anti-matrix metalloproteinase (anti-MMP) antibodies have been shown to be directed against MMP-1 and MMP-3; these antibodies prevent ECM degradation and thus may promote fibrosis [36]. Anti-platelet-derived growth factor (anti-PDGF) antibodies have been reported to recognize and activate the human PDGF receptor and to stimulate reactive oxygen species (ROS) and collagen production [37]. However, these findings could not be reproduced in subsequent studies [38].

Fibrosis

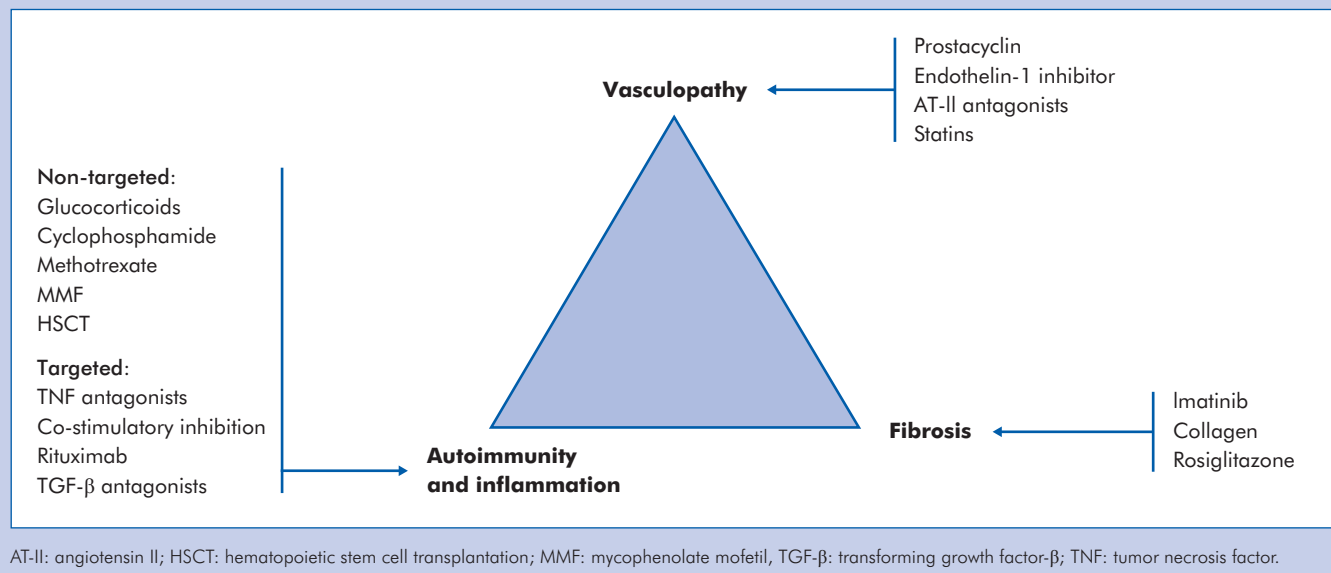
Fibrosis is a complex biological process involving an acute inflammatory response and subsequent overproduction of ECM proteins. One underlying concept is the activation and stimulation of fibroblasts by as yet unknown stimuli. Another concept is the endothelial–mesenchymal transition (EMT), in which endothelial cells are transformed into matrix-producing cells such as myofibroblasts. A third, yet unproven, theory is the recruitment of circulating fibrocytes [39]. Fibrocytes are a bone marrow-derived cell type of the monocytic lineage that have a physiological function in wound healing and might be of importance in fibrosis. Cytokines, especially TGF- β , have an important role in the development of fibrosis. The transcription factor T-box expressed in T cells (T-bet) has recently been identified as an important regulator of skin sclerosis in the bleomycin-induced animal model of SSc. Knockout of T-bet, the main regulator of the Th1 immune response, led to skin fibrosis via an IL-13-dependent pathway [40].

Taking into account that ECM undergoes a constant turnover, impaired breakdown of the matrix may also result in fibrosis. More specifically, the inhibition of metalloproteinases by tissue inhibitors of metalloproteinases (TIMPs) results in reduced ECM breakdown. In SSc, levels of both TIMP-1 and TIMP-2 are raised in the serum and correlate with disease severity [41]. SSc fibroblasts express higher levels of TIMP-1 mRNA compared with healthy controls [42].

Therapeutic strategies

The current therapeutic strategy for SSc usually includes the use of calcium channel antagonists for vasodilation and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist for the prevention and treatment of renal crisis (Figure 2). Further treatment depends on the stage of the disease and the organs involved. Prostacyclin and ET-1 receptor antagonists are used for pulmonary arterial hypertension and digital ulcers. The chemotherapeutic agent cyclophosphamide has shown to be of benefit in lung fibrosis and skin involvement and is usually given in diffuse and progressive disease. In selected patients, stem cell transplantation has been shown to

Figure 2. Therapeutic strategies in systemic sclerosis.



be beneficial. The optimal time-points at which to treat, and the optimal substance to use, have not yet been established. Future therapies will hopefully be more targeted, organ-based, and disease-stage-adapted. Better understanding of the cytokine environment may permit the adaptation of available treatment options to the individual patient.

Vasoactive substances

Vascular damage occurs in the first phase of SSc and is one of the main features of the disease. Digital ulcers or Raynaud's phenomenon lead to a reduction in quality of life in most SSc patients. Pulmonary hypertension and renal crisis are life-threatening manifestations of SSc.

New drugs have been developed that act directly on the vessel wall. The ET-1 inhibitor bosentan is currently approved for use in pulmonary hypertension (grade 2–4) and the prevention of digital ulcers in SSc. The efficacy of bosentan was illustrated in an investigation demonstrating long-term improvement and disease stability in patients with grade 3 pulmonary hypertension [43]. This was confirmed in another study in which bosentan improved New York Heart Association class and hemodynamics [44]. Sitaxsentan and ambrisentan are two other ET-1 inhibitors that are successfully used in pulmonary hypertension.

Continuous intravenous epoprostenol is effective in the treatment of Raynaud's phenomenon secondary to SSc; it reduces the frequency and severity of attacks and prevents formation/induces the healing of digital ulcers. In a controlled trial, a positive effect on exercise capacity and cardiopulmonary hemodynamics has been demonstrated [45]. Patients with connective tissue-associated pulmonary hypertension have also benefited from a treatment with sildenafil, a phosphodiesterase inhibitor [46].

Immunosuppression

Immunosuppressive therapy is used in a substantial group of SSc patients [47]. Although no clear evidence for efficacy has been reported, up to 60% of SSc patients receive glucocorticoids. In >40% of cases, an immunosuppressive treatment is given, mostly consisting of cyclophosphamide, methotrexate, azathioprine, or hydroxychloroquine. Thus far, clear evidence of efficacy exists only for cyclophosphamide, which has been shown to be effective in SSc lung disease and skin involvement [48]. However, the positive effects seem to disappear 1 year after treatment cessation [49]. Methotrexate is widely used in SSc patients with diffuse cutaneous disease. A recent case series showed indirect evidence of its efficacy, with a good response of skin involvement that worsened after withdrawal of the treatment [50]. Mycophenolate mofetil (MMF) has shown positive effects on SSc-related interstitial lung disease in several retrospective studies [51,52]. In addition to its immunosuppressive effect, MMF also seems to have an inhibitory effect on TGF- β . A prospective, Phase I, open-label study of MMF is currently ongoing (www.clinicaltrials.gov identifier: NCT00433186). Another ongoing study is investigating treatment with high-dose intravenous immunoglobulins (www.clinicaltrials.gov identifier NCT00348296).

Targeted therapy

In several retrospective case series, TNF- α inhibitors have been found to have positive effects on arthritis in SSc [53]. Interestingly, in these patients, the skin score also improved. In a prospective, open-label trial, 16 patients with diffuse SSc received monthly infliximab infusions [54]. In that study, the skin score did not improve after 26 weeks. No large clinical trials using TNF- α are being performed at present.

Abatacept is a recombinant fusion protein that blocks T cell activation. It has recently been approved by the US Food and Drug Administration for the treatment of patients with RA. Inhibition of T cell activation with abatacept may also be efficacious in the treatment of patients with diffuse SSc. A randomized, double-blind, placebo-controlled clinical trial of abatacept versus placebo in patients with diffuse SSc is ongoing (www.clinicaltrials.gov identifier: NCT00442611).

“Vasoactive agents are used to treat and prevent Raynaud’s syndrome, pulmonary hypertension, and renal crisis in SSc.”

Rituximab is a monoclonal antibody directed against the CD20 transmembrane protein present on B cells [55]. Given the potential pathogenetic role of autoantibodies, B cell depletion is also under focus in SSc. In a mouse model of SSc, rituximab was found to cause reduction in skin fibrosis, autoantibody titers, and hypergammaglobulinemia. However, this positive effect was not observed in the chronic phase of the disease. A recent study in eight patients receiving rituximab demonstrated an improvement in the skin score, dermal hyalinized collagen content, and numbers of dermal myofibroblasts at 24 weeks [56]. However, a more recent study in 15 patients with diffuse cutaneous SSc found no positive improvement in skin fibrosis or autoantibody titer with rituximab treatment, despite efficient B cell depletion being demonstrated [57].

A neutralizing anti-TGF- β antibody has been studied in the early stage of diffuse SSc in 45 patients. The skin score improved in both the study and the placebo groups (a significant difference was not observed) [58]. Currently, the p144 peptide inhibitor of TGF- β is being explored for topical use in SSc (www.clinicaltrials.gov identifier: NCT00574613).

Antifibrotic agents

Imatinib mesylate

Imatinib was developed to target the tyrosine kinase ABL. It is being used as an effective treatment for chronic myelogenous leukemia, during which ABL is translocated from chromosome 9 to 22. In addition to ABL, imatinib targets other kinases such as c-Kit and the PDGF receptor.

Imatinib may be effective in SSc as fibroblasts can be activated by tyrosine kinases such as the PDGF receptor. In addition, Abl plays a role in the downstream signaling of TGF- β [59]. Data from animal models have demonstrated a reduction in fibrosis in bleomycin-induced lung and skin damage, as well as in obstructive renal fibrosis [60–62]. Inhibition of Abl and PDGF signaling by imatinib can also reduce fibrosis in later stages of SSc [63]. In five patients with SSc interstitial lung disease treated with 200 mg imatinib per day and cyclophosphamide intravenously every 3 weeks, only

one patient had an improvement in lung function [64]. In an ongoing Phase II trial, 18 patients have initiated treatment, receiving 400 mg imatinib per day. Acceptable tolerance and an improvement of the modified Rodnan Skin Score (mRSS) has been shown in an interim analysis [65]; however, the latter did not reach statistical significance. In a report describing two patients treated with imatinib, a clear improvement in skin status and resolution of ground-glass opacities on chest computed tomography (CT) scan were observed [66]. Imatinib has also been used in nephrogenic fibrosis, a disease with a similar phenotype to SSc. A reduction in fibrosis has been observed in this condition [67].

Oral collagen

Collagen has been identified as a possible autoantigen in SSc. The rationale for the oral application of type 1 collagen is the induction of tolerance. In a prospective, multicenter trial, 168 patients were treated with 500 μ g/day of type 1 collagen [68]. Although no statistical significance was demonstrated for the primary endpoints, the skin status improved significantly in the late-phase diffuse SSc subgroup.

Rosiglitazone

Rosiglitazone is an agent that was developed for the treatment of type 2 diabetes. It is an agonist of the peroxisome proliferator-activated receptor (PPAR). PPAR stimulation abrogates collagen expression and TGF- β -dependent myofibroblast differentiation. It has now been demonstrated in the bleomycin mouse model that rosiglitazone is effective in reducing skin inflammation and dermal fibrosis [69].

Relaxin

Relaxin is a physiologically occurring protein that exhibits antifibrotic properties via downregulation of collagen in fibroblasts, increasing the expression of MMPs, and inhibition of TGF- β . These effects have been shown in the bleomycin model of lung injury [70]. However, the results of a Phase III, randomized, double-blind controlled trial showed no effect of relaxin on skin, lung, or functional disability [71]. Moreover, it was associated with a higher rate of adverse events than placebo treatment.

Cellular therapy

Autologous and allogeneic hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) in autoimmune diseases is aimed at resetting the dysregulated immune system by immunoablative therapy followed by reinfusion of previously isolated HSCs [18]. HSCs may originate either from the patient him/herself (autologous) or from a human leukocyte antigen (HLA)-matched individual, typically a family member (allogeneic). The advantages of autologous HSCT are a lower

treatment-related mortality (TRM) rate due to the absence of a graft-versus-host disease (GVHD), which occurs in 20–40% of allogeneic HSCT. On the other hand, a postulated graft-versus-autoimmunity effect (analogous to a graft-versus-leukemia effect) has been suggested to occur in allogeneic HSCT. Prospective, multicenter trials in SSc are currently ongoing for autologous HSCT whereas only case reports are available for allogeneic HSCT.

Autologous HSCT is a multistep procedure. Firstly, HSCs are mobilized by administration of intravenous cyclophosphamide and granulocyte-colony stimulating factor (G-CSF). HSCs are then collected by leukapheresis. After conditioning with high-dose cyclophosphamide, HSCs are reinfused to shorten aplasia and thus the risk of bleeding or infection.

The main mechanistic effects in autologous HSCT are achieved by eradication of autoaggressive “effector T and B cells” and the induction of regulatory T cells. There is evidence that autologous HSCT may restore tolerance, despite the use of host cells.

“Currently, there are three ongoing, prospective, multicenter studies investigating the safety and efficacy of autologous HSCT in SSc”

In a French–Dutch collaborative study involving 26 patients for whom long-term follow-up data were available, event-free survival, defined as survival without mortality, relapse, or progression of SSc resulting in major organ dysfunction, was 64.3% (95% confidence interval [CI] 47.9–86%) at 5 years [72]. Skin thickening and performance status improved markedly, and organ dysfunction stabilized. Similar results have been reported in a North American study [73]. However, relapses occurred in one-third of the cases, typically after 2–4 years [72]. The TRM rate in the autologous setting is approximately 6%. With growing expertise in HSCT, further reduction in TRM may be feasible, especially if patients with less advanced SSc are treated.

Currently, there are three ongoing, prospective, multicenter studies investigating the safety and efficacy of autologous HSCT in SSc. A total of 146 patients have thus far been randomized in the European ASTIS (Autologous Stem Cell Transplantation International Scleroderma) trial, and accrual is expected to be complete by the end of 2009. The two other trials are SCOT (Scleroderma Cyclophosphamide or Transplantation Trial) and ASSIST (American Scleroderma Stem Cell versus Immune Suppression Trial).

In allogeneic HSCT, stem cells are obtained from matched family members or matched unrelated donors. The conditioning regimen includes cytotoxic agents such as fludarabine or busulphan and anti-thymocyte globulin with or

without total body irradiation. The conditioning treatment is mainly performed to allow significant engraftment of the donor HSCs. In order to reduce TRM, non-myeloablative regimens are increasingly applied. Immunosuppressive therapy with methotrexate or cyclosporine is given to prevent GVHD.

Thus far, the available data are from case series, which demonstrate that allogeneic HSCT can lead to persistent remission or cure of the underlying autoimmune disease. Four patients with SSc have been treated with allogeneic HSCT to date. The first two, who received myeloablative conditioning, showed improvement of skin thickening and resolution of ground glass opacities on chest CT [74]. However, one died from *Pseudomonas* sepsis 18 months after the treatment. Two other patients, who underwent non-myeloablative conditioning, remained in full remission for 3 years without signs of GVHD [75,76]. Given the lack of available matched donors, the risks associated with allogeneic HSCT, and the excellent results with autologous HSCT, it is unlikely that prospective trials of allogeneic HSCT will be performed in SSc.

Mesenchymal stem cell transplantation

MSCs are bone marrow-derived stromal cells that give rise to cells such as chondrocytes and osteocytes. In addition to their differentiation capacity, MSCs have immunomodulatory effects and are bystanders in hematopoiesis. Therapeutic benefit of MSC transplantation (MSCT) has been shown in GVHD, which is considered to share several pathogenic features with SSc [77]. Five patients suffering from severe, diffuse SSc were elected for this treatment [78]. MSCs were obtained by bone marrow aspiration of cross-gender related donors. Adherent cells were cultured in fresh frozen human plasma and platelet lysate. All five patients showed an improvement of their skin status and acral ulcers following MSCT. Organ functions stabilized and no treatment toxicity occurred.

Conclusions and future perspectives

Despite being a rare and complex disease, important new findings have been made in SSc in recent years involving the two pathogenic aspects of vasculopathy and cytokine/immune dysregulation. New treatment options target both of these aspects and are either directed at a broad range of targets (stem cell transplantation) or more focused on a single pathway. The major task for the near future will be to design patient-adapted treatment, taking into account age, symptoms, and disease state and subtype.

Disclosures

The authors have no relevant financial interests to disclose.

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METEOR as an Information Technology Tool to Assess Rheumatoid Arthritis Disease Activity in Clinical Practice and Improve Patient Outcome via Tailor-Made Treatment

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The management of patients with rheumatoid arthritis in clinical practice is a long-term task requiring frequent patient-physician consultations to collect and follow-up detailed clinical and biological information, as well as to regularly assess and/or adjust treatment. International expert rheumatologists have designed a custom-made software tool, the METEOR (Measurement of Efficacy of Treatment in the “Era of Outcome” in Rheumatology) application, to easily collect critical information with the objective of improving patient care. The follow-up of every patient – including assessments of disease activity, functional status, and treatments – can be visualized individually on the computer screen in the consulting room by both the patient and rheumatologist, and trends of disease activity over time can be discussed together, allowing a carefully tailored treatment plan to be established. Moreover, collected data can also serve as an anonymous global database in which the results observed in a given patient can be directly compared with those of similar patients followed-up and treated by other rheumatologists from the same hospital or city, country, or the entire METEOR community. *Int J Adv Rheumatol* 2009;7(2):44–50.

Context: the need for close monitoring of disease activity in rheumatoid arthritis

Rheumatoid arthritis (RA) is a common debilitating disease in Europe facing people of all ages, with an increasing number of patients seeking medical assistance. Numerous treatments and management strategies are available today, with an extraordinary potential to control signs and symptoms and functional impairment – provided that treatment is adequately prescribed, patients are regularly monitored, and treatment is

adapted accordingly. In particular, there have been many studies clearly showing that tight control of disease activity, based on treatment adjusted according to repeated clinical assessments and a predefined goal, can not only lead to an improved well-being of patients, but also to a significant decrease in functional disability [1–8].

One of the most relevant examples of the effects of a “tight-control strategy” on patient outcomes stems from the CAMERA (Computer-Assisted Management for Early RA) study: 299 patients with early RA were randomized between conventional and intensive treatment, both aiming at achieving remission. Interestingly, the same drug treatments were used, but they were applied either in a conventional or an intensive scheme, the latter based on systematic use of an objective computer

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decision program. Clinical data that were used by the algorithm were swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and the Visual Analogue Scale (VAS) for general well-being. After 2 years, long-lasting remission (defined as no swollen joints and two out of three of the following: number of tender joints less than three, ESR <20 mm/h, VAS general well-being score <20/100 for ≥6 consecutive months) was achieved by 50% of the patients in the intensive follow-up arm compared with 37% in the usual care group ($p=0.029$) [8]. However, such a precise measurement of disease activity requires the use of well-defined tools based on clinical evaluation, self-assessment by the patient of their health condition, and results of laboratory tests. These tools, like the disease activity score (DAS) [9], the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) [10], can easily be perceived as too time-consuming and for that reason be ignored by the practitioner, leading to a suboptimal standard of care for patients. However, assistance by a good information technology (IT) tool might reduce the burden of care substantially and may, in the long-term, not be more time consuming than running a clinical practice without such a formal assessment.

“Tight control of RA disease activity leads to improved patient well-being and a significant decrease in functional disability”

The Merit Foundation and the METEOR tool

Recognizing that a consistent means of capturing and sharing information on patient treatment was lacking, the Merit Foundation was established by several experts in RA as a non-commercial, international medical organization with the aim of designing and providing a free internet-based application that could be used by patients and rheumatologists to monitor disease over time.

The software itself, named METEOR (an acronym for “Measurement of Efficacy of Treatment in the ‘Era of Outcome’ in Rheumatology”), is an on-line tool that has been designed to improve patient care by supporting and assisting rheumatologists on both a day-to-day and long-term basis. METEOR aims to capture patient data and record outcomes over time, allowing the visualization of trends by the patient and treating physician, and to help rheumatologists in setting goals and visually sharing treatment progress with the patient. Data are captured in a central database of anonymous records. The rheumatologist has the option to compare data from their own practice with those of all patients entered in the METEOR

database as a benchmark. In addition, the database can be used for publications, case studies, or general research investigations by any of the rheumatologists involved in the process. The international METEOR scientific committee reviews and approves all research proposals.

“METEOR is an on-line tool that captures RA patient data and records outcomes over time”

The software itself, which has been engineered by IBM (New York, NY, USA) according to requirements made by the expert rheumatologists of the international board established by the Merit Foundation, is highly self-explanatory, user-friendly, and web-based, and does not require any specific software to be installed on the computer nor advanced IT knowledge by the user. It has been designed to be used via the internet with a very high level of security and confidentiality: the system requires a username, password, and encryption key, provided by the local administrator, to be able to collect and review patient data. The level of accessibility depends on the role that has been assigned to that specific user. The site (hospital)-specific encryption key is used to ensure that data identifying a patient – such as name and date of birth – can only be seen by the physicians treating that patient. The encryption key remains in the hospital and is never transferred. Patients cannot be identified from data in the METEOR system without that key. A professional hosting company, providing both a high level of security and good availability, runs the METEOR system and database. By logging into the application, the user accepts the term and conditions regarding confidentiality.

METEOR: specific modules

Different modules are available for the physician while examining his/her RA patient. The “Patient Characteristics” window will display the usual basic demographic data as well as characteristics of the disease; for example, date of symptoms onset, rheumatoid factor status, anti-CCP antibodies, smoking status, diagnosis, weight, and height (**Figure 1**).

The health assessment questionnaire (HAQ) module is an interactive questionnaire that automatically calculates, displays, and stores the functional status of the patient by simply ticking the boxes.

It is possible to allocate limited user access to patients, if local hospital policy permits this, using a unique patient personal identification number (PIN) code, password, and encryption key. The HAQ can be completed by the patient prior to the consultation, either from their personal computer (PC) via the internet, or, for example, on a dedicated PC in the waiting room, thus saving precious consultation time.

Figure 1. METEOR application: the “Patient Characteristics” module.

Logout Rheumatology Record Close

METEOR Welcome Search Patient Menmal G. Reports Profile

Patient : 1234 Gérard Menmal

Menu

- New visit
- Patient Characteristics**
- HAQ
- DAS
- Drugs
- Overview
- Graphics
- Print Patient Overview
- Close

Visits

- 2001-01-05
- 2001-01-03
- 2001-01-02
- 2001-01-01

Patient Characteristics

Patient Card

PinCode 1234

Identifier 1234

Lastname Menmal

Firstname Gérard

Sex male

Birthday 1951-10-02

Street 10 rue fret

Zip Code 75000

City Paris

Country France

Telephone

Email

Password

en-Idencrypt key

Patient Additional Details

Marital Status unknown

Debut of Symptoms 2000-01-01

Date of Diagnosis 2000-02-02

Smoking never smoked

Rheumatoid Factor present ☒

Anti-CCP present ☒

Erosions present ☒

Weight (in kg) 85

Height (in cm) 175

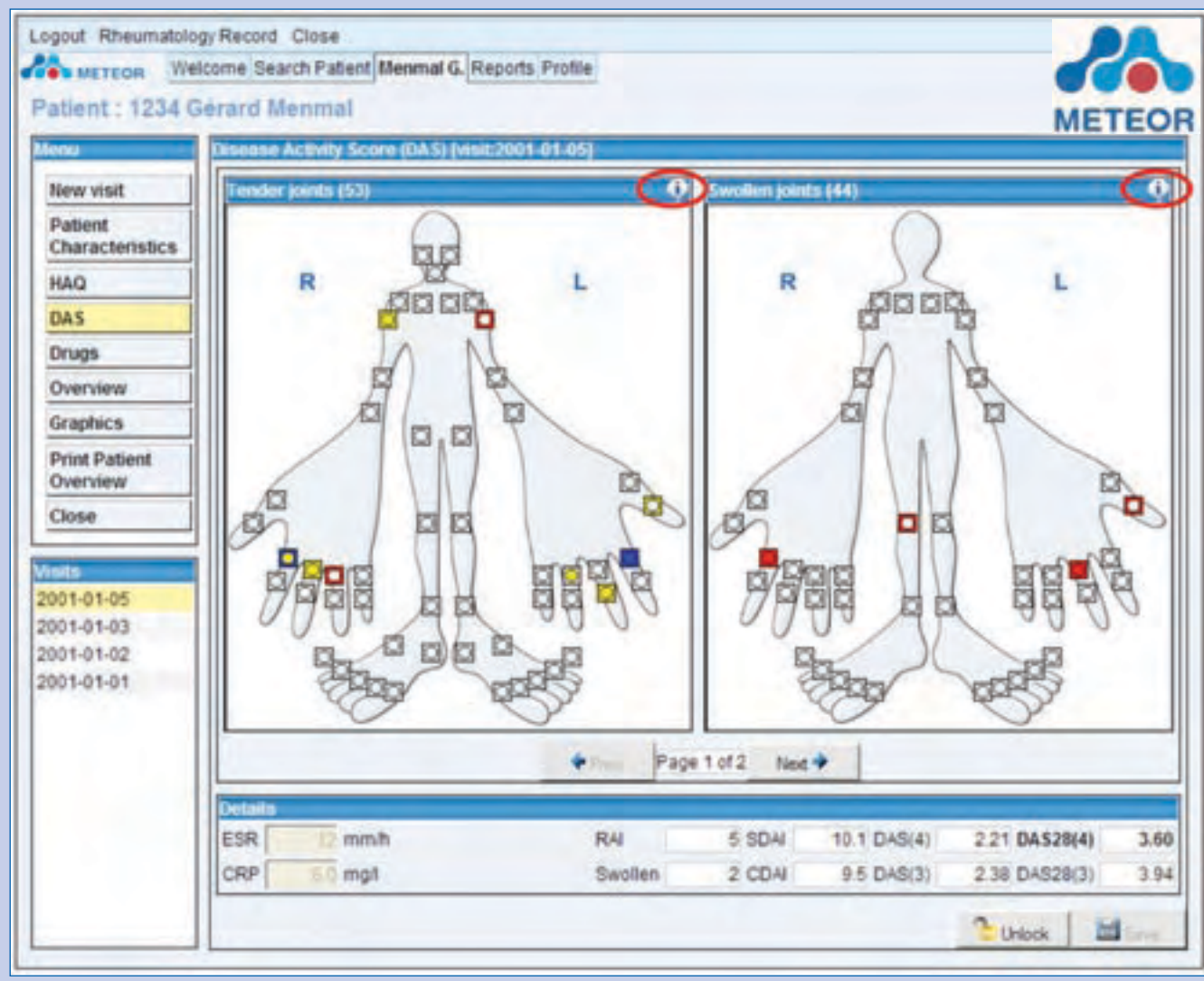
The central module is the “Disease Activity” page, which displays two mannequins (one for the tender joints, another for the swollen joints), with each joint slightly enlarging as the mouse arrow hovers over it and information about tenderness and swelling being captured by simply clicking on the joint (Figure 2). Information about the status observed for each individual joint at the patient’s previous visit is also shown by the color of the square surrounding the joint of interest. The mannequin profile can be changed and adapted by each individual clinician according to his/her clinical preference; different presets show either 28 or 44 joints, and diverse disease activity indices such as DAS, DAS28, CDAI, or SDAI can be selected. The METEOR application also captures information on drug treatment for RA in a dedicated module. Entering treatment modalities is facilitated by showing the closest matches on a drop-down menu as the user is typing the first few letters of the desired drug. After selection of the drug, the standard prescribed dosages and modalities of administration are presented, although

these can be modified according to any individual specificity (Figure 3). The time and reason for treatment discontinuation may also be collected, either recording the date of the current consultation if treatment is modified during the visit, or noting an earlier date if the treatment has previously been stopped (for example if an adverse event has occurred). Patient comorbidities can also be entered and recorded in a specific area of the “overview module”, in accordance with the International Classification of Diseases (ICD-10) codes.

“METEOR modules record data on patient characteristics, disease activity, and drug treatment history”

All entered data will then assist the physician in tailoring treatment by visualizing and comparing interventions (e.g. drug prescriptions and intra-articular injections of corticosteroids)

Figure 2. METEOR application: the “DAS” module.



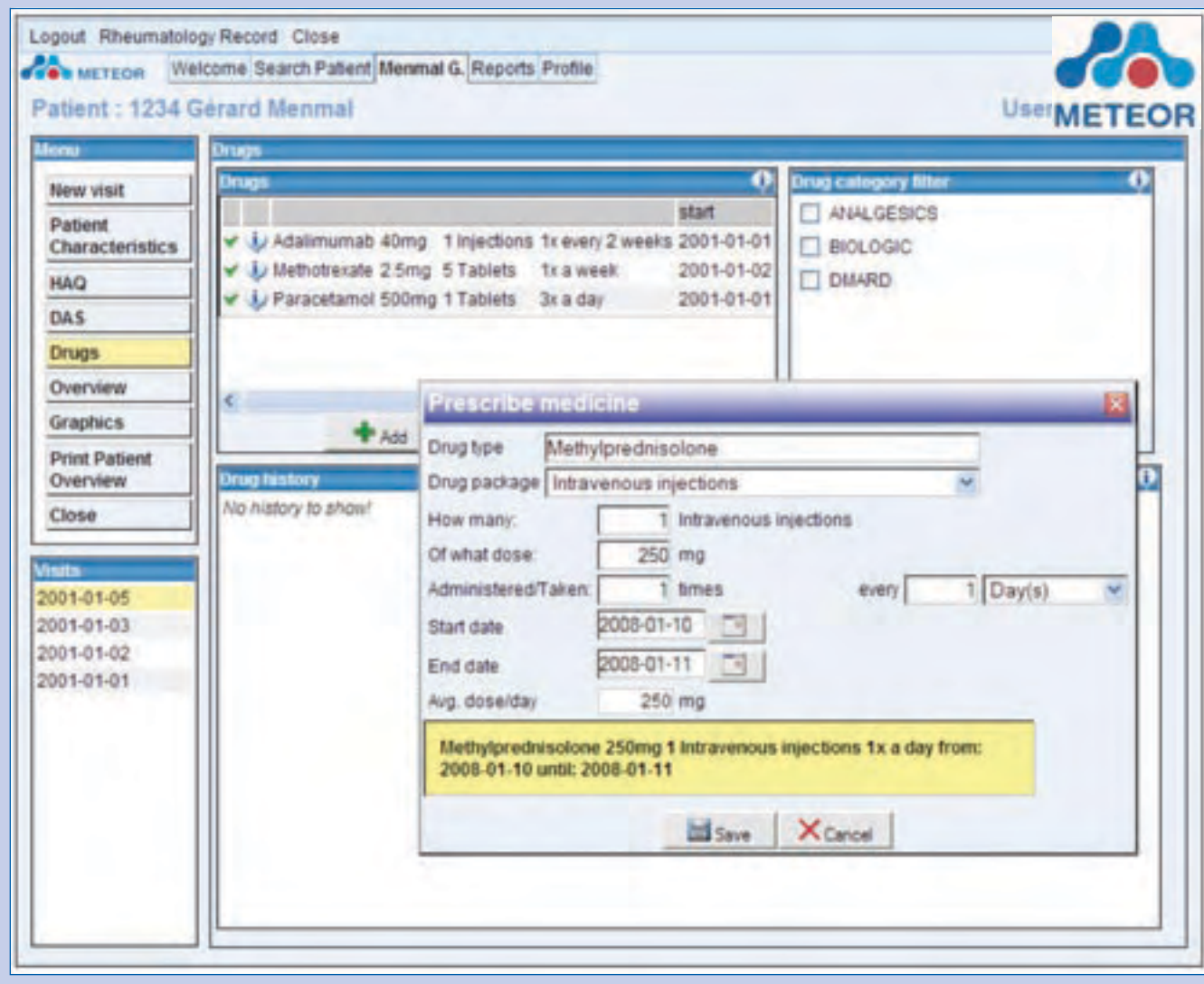
with the trends of disease activity and functional status over time (Figure 4). This information, along with graphical representations, can be printed and stored in the patient dossier or sent to the general practitioner. There is also an open text page available for annotating specific information; this will be stored locally and will serve as a reminder to the physician during subsequent visits.

METEOR as a way to improve the patient's self-management

The METEOR application has been specifically designed to be used during the examination time of the patient, at no additional time cost. Once the patient has been recorded in the system during his/her first consultation, adding a new visit takes only a few seconds, and the critical clinical and biological information can be entered in a few mouse clicks on the dedicated page,

notably via the interactive mannequin to specify and count the tender or swollen joints, which will be automatically used to calculate and display the value of the disease activity score for that patient on the same page and on follow-up graphs or tables. Moreover, a personal PIN code, password, and encryption key will be given by the rheumatologist to their patients, allowing the patient to access and monitor part of their own medical records from home, including the HAQ, which measures the degree of functional disability due to the disease, and several VAS measures that will assess the respective levels of pain and disease activity as evaluated by the patient themselves. This specific feature offered by METEOR will help the patient improve self-management as self-monitoring from home can be visualized graphically and discussed together with their physician on the next visit, and will serve as a basis to adapt treatment accordingly.

Figure 3. METEOR application: the “Drugs” module.



METEOR as a global benchmark tool to share and compare standards of care and results

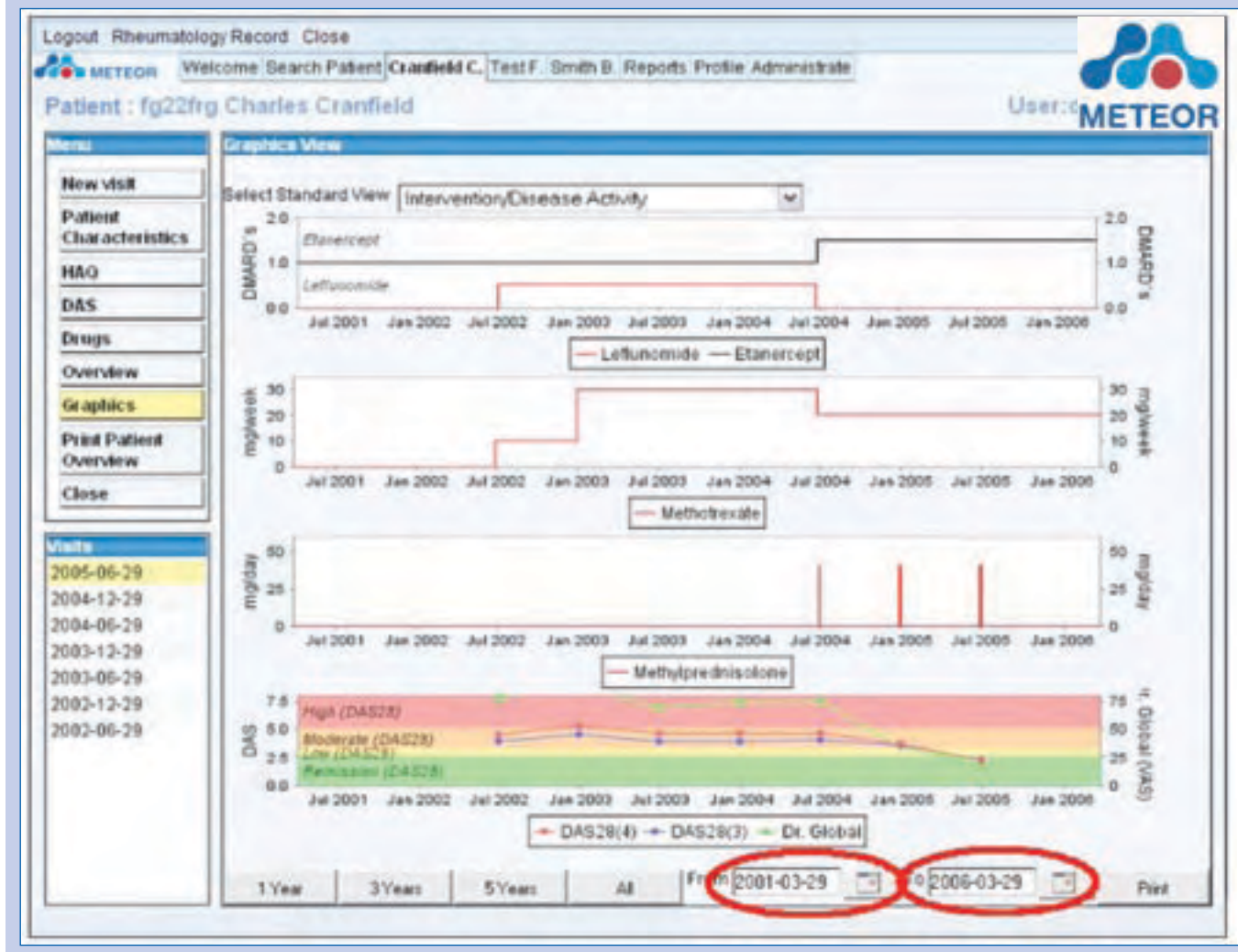
METEOR provides another specific and attractive characteristic: data entered by each user of the system will provide an anonymous global database aimed at benchmarking the results observed in a specific patient in comparison with similar patients followed up and treated by other rheumatologists from the same hospital, city, country, or indeed the entire METEOR community. The highly detailed and user-friendly report function of the tool will enable rheumatologists to learn from others about the best treatment for their patients, and to monitor patients' progress and benchmark responses to treatment relative to other patients, using simple graphics on a PC screen within the consulting room. Local and regional experiences of disease management and their

respective outcomes can thus be compared with those from other regions or countries, with the overall aim of achieving an optimal standard of care for RA.

Benefits from METEOR use

Physicians and patients are now collaborating on individual treatment strategies, according to the patient's history as displayed in a single view on a PC in the consulting room. Feedback suggests that both patients and physicians like using the new tool. It allows physicians to change their daily practice; for example, deciding upon a treatment change based on patient-derived outcomes such as the HAQ value. The tool enables easier capture, visualization, and integration of this information into the overall evaluation process. Thus, physicians find it easy and quick to use and patients feel they are participating in their own treatment.

Figure 4. METEOR application: the “Graphics” module.



Clinicians now have access to thousands of anonymous patient records, covering several countries and many hospitals (>3000 patients have been included at this time, with eight countries thus far actively participating in the project after approximately 1 year of availability). They can learn from one another on the best treatment for their patients.

Other available similar tools and projects

METEOR is not the first, nor the only, tool that has been developed to follow patients with RA and collect information about their health status, disease activity, and medications. In The Netherlands for example, an initiative named Arthritis Disease Activity Information System (ADAISY) has been used since 2004, and is based on a software designed to capture data from patients with rheumatic diseases (ankylosing spondylitis and psoriatic arthritis in addition to RA).

Another tool developed in Boston, MA, USA, called the Rheumatology OnCall (ROC) application, summarizes, on a single web page, the clinical, biological, and radiographic data collected during an RA patient visit, as well as current and past drug treatment history and trends of disease activity over recent time. A recent study conducted to evaluate feasibility and utility of the ROC application concluded that it may be useful in daily clinical practice, provided that users' acceptance is obtained and access to electronic medical record is available in the clinical setting [11].

Other countries have also based the nationwide monitoring of patients with RA on an electronic medical record, for example DANBIO in Denmark. For all Danish practitioners, registration of any newly referred RA patient, or of any RA patient in whom biological treatment has been decided upon, has been mandatory in DANBIO since 2006. This has resulted in a very high registration rate, estimated at >90% of all RA patients.

An expected advantage of METEOR over these other apparently similar projects is that it is free of charge, available worldwide via the internet to any interested user, and enables immediate benchmarking in comparison with other similar patients treated in the same hospital, country, or entire METEOR community to be conducted.

“Other IT tools and projects for extensive data collection in RA are also available, for example ADAISY, DANBIO, ROC, and QUEST-RA”

Other projects have also been undertaken with the objectives of describing and analyzing characteristics of RA patients as well as therapeutic behaviors across different countries in standard clinical care. The most famous example in this context is the Quantitative Patient Questionnaires in Standard Monitoring of Patients with RA (QUEST-RA) project, which reviewed 4363 patients from 48 centers in 15 countries between January 2005 and October 2006 [12]. METEOR will enable similar descriptive, as well as more detailed, analyses of data, with the advantage that the crucial information will be collected at no additional time cost for the rheumatologist, serving for both regular follow-up and central database extension purposes.

Possible limitations of the METEOR tool

Although the METEOR tool has been designed – from the very early stages – with the ambition of being an ideal compromise between feasibility (meaning a limitation of time needed to complete the assessment pages) and relevancy (requiring a certain amount of collected information to ensure appropriate follow-up and guidance in therapeutic decisions), any extra time required to initiate the process during an initial consultation may be considered a limitation. However, one may argue against accessory time consumption if the collection of data is performed parallel to the usual standard of care.

Some may criticize that certain components of the disease, such as radiographic follow-up, quality of life, or cost-related information, are not included in the spectrum of collected data. However, features including radiographic follow-up may be added to new releases of the application, as a regular update of the software, based on feedback from the users, is conducted periodically.

In addition, although METEOR is provided free of charge to any interested user, another technical or financial limitation that could apply (to developing countries in particular) is that using METEOR requires both a computer and an internet connection, or at least a local network to ensure appropriate communication between the user and the METEOR server.

You can submit comments and questions on this article at:

www.advancesinrheumatology.com



Disclosures

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Pain Control Challenge in a Chronic Inflammatory Demyelinating Polyneuropathy with Systemic Lupus Erythematosus: A Case Report

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A PDF of this case study is also available free from
www.advancesinrheumatology.com

The co-existence of systemic lupus erythematosus (SLE) and chronic inflammatory demyelinating polyneuropathy (CIDP) is rare but has been documented [1]. Pain can be a disabling symptom in both of these disorders. Neuropathic pain combined with musculoskeletal pain can make patient management difficult.

SLE is a chronic, autoimmune, inflammatory disease that can potentially affect every organ system. The disease results from antibody reactivity with components of the cell's nucleus and multisystem microvascular inflammation [2–4]. There may be multiple pathways that can lead to pain, with arthralgia being a very common complaint.

CIDP is characterized by symmetrical weakness in both proximal and distal muscles that persists for >2 months [5]. It is thought to be caused by demyelination in the peripheral nervous system. This peripheral neuropathy can be accompanied by disabling neuropathic pain, which has only recently been recognized as a significant symptom in CIDP patients [6]. The present case report highlights both challenges and success in treating pain in a patient with comorbid SLE and CIDP.

Case description

A 25-year-old African American female presented with lightheadedness, malaise, myalgia, and stiffness in March 2006. The first signs of weakness were difficulties in picking

up her child and getting up from a chair. This progressed to quadriplegia over the following 3 weeks. At 5 weeks after presentation she developed dysphagia, extraocular muscle weakness, pupillary dilatation, and subsequent respiratory failure. She was intubated, and mechanically ventilated.

Four weeks later, electromyographic (EMG) findings were consistent with acute IDP (AIDP). Muscle biopsy of the left deltoid showed a non-inflammatory necrotizing myopathy. Sural nerve biopsy showed the presence of a few myelin ovoids, suggesting an axonopathy. Smith (anti-Sm), antinuclear (speckled), anti-Jo-1, and ribonucleoprotein (RNP) antibodies were present. The erythrocyte sedimentation rate (ESR) was elevated at 115–130 mm/h. After treatment with high-dose prednisone and intravenous immunoglobulin (IVIg) the patient began to regain muscle strength. Eventually she was able to sit herself and ambulate without assistance. By August 2006, she showed only mild residual difficulty in negotiating stairs and was discharged home.

In October 2006, the patient had a relapse of her previous symptoms. Her chief complaint was severe (10 out of 10 on the Visual Numeric Scale [VNS]) pain in multiple joints. She described it as “continuous, excruciating, muscle tearing, and stabbing” accompanied by a tingling and burning sensation in a stocking-glove distribution. She noted stiffness in all of the joints, lower extremity weakness, shortness of breath, and bilateral lower limb swelling. EMG findings met the criteria for CIDP. Urinalysis

revealed proteinuria and the patient was diagnosed with early membranous lupus nephropathy, confirmed by renal biopsy. She was treated with prednisone and mycophenolate mofetil. Her pain only improved with intramuscular injections of fentanyl. She eventually self-discontinued all medications.

“The present case report highlights both challenges and success in treating pain in a patient with comorbid SLE and CIDP”

In December 2007, the patient was brought to the hospital with constant severe pain accompanied by bilateral hand tingling, bilateral lower extremity paresthesia, and anesthesia up to the knees. She complained of headache and blurry vision for 1 week, and severe pain (10 out of 10 on the VNS) in multiple joints. A magnetic resonance imaging scan of the brain/orbit was within normal limits. Lumbar puncture revealed increased cerebrospinal fluid (CSF) pressure with elevated protein levels. The patient was diagnosed with pseudotumor cerebri and optic neuritis. Multiple electrodiagnostic studies showed no significant change from prior findings. She was treated with intravenous solumedrol, followed by oral prednisone and IVIg. Her pain was treated with gabapentin, nortryptiline, long-acting morphine, a fentanyl patch, and short-acting morphine for breakthrough pain. Her symptoms only minimally improved on this regimen. Two weeks after the first IVIg treatment, the patient was admitted to the rehabilitation unit.

On rehabilitation admission, her pain was 10 out of 10 on the VNS. She was bed-bound with a motor strength of less than 2 out of 5 on the Medical Research Council Scale in the bilateral upper and lower extremities. The decision was made to discontinue all of the current pain medications and to start methadone, which was titrated up to 10 mg orally three times daily. The patient's response to methadone was dramatic with resolution of her pain within 4 days. There was concomitant improvement in joint stiffness, numbness, and burning. Her pain was zero out of 10 on discharge.

Discussion

Pain occurs in up to 90% of patients with SLE. In a study of 106 patients with SLE, pain scores correlated with perceived disability and psychosocial adjustment [7]. Painful joints are the most common presenting symptoms of SLE with reported frequencies of 76–100%. The patient's complaint of pain may exceed the degree of synovitis.

Approximately two-thirds of people with SLE have neurological or psychiatric manifestations [5]. The most common neurological manifestations are the cognitive

dysfunction and headache [8]. Cranial or peripheral nerve pathology occurs in 10–15% of patients with SLE, usually concomitant with disease exacerbation [8]. The most common peripheral patterns are pure or predominantly sensory neuropathy in a stocking-glove distribution, mononeuropathy (simplex or multiplex), and ascending polyradiculoneuropathy. CIDP is a rare, but well-recognized, neurological complication of SLE [9].

N-methyl-D-aspartate (NMDA) receptors are widely distributed in the central and peripheral nervous systems and are present in the hippocampus, amygdala, and hypothalamus. Excessive activation of these receptors can result in neuronal activation and possibly excitotoxic cell death [10]. A subset of antibodies has been identified in the serum and CSF of SLE patients that are directed against NMDA receptors, specifically the NR2A and NR2B subunits. These antibodies may have adverse effects on pain processing, cognition, and emotional behavior [11].

Pain can be one of the most disabling symptoms of peripheral neuropathy. Nerve injury results in an upregulation of NMDA receptors through repeated firing of the peripheral afferent fibers and release of glutamate. The pathophysiology of neuropathic pain following peripheral nerve injury includes peripheral sensitization, central sensitization in the spinal cord or brain, and hyperactivity of central pain transmission neurons [12,13]. In inflammatory neuropathy, cyclooxygenase-2 and proinflammatory cytokines have been found to be upregulated in nerve biopsy resulting in peripheral sensitization [14]. Central sensitization involves the sensitizing of spinal cord dorsal horn neurons by released glutamate (following peripheral injury), which acts on postsynaptic NMDA receptors and substance P [12,13]. This results in greater than expected peripheral pain [11]. In CIDP, weakness and paresthesia are the most common symptoms, but pain can be a prominent feature [15]. It is known that pain in CIDP might not respond to tricyclic antidepressants, antiepileptic drugs, or synthetic opioid agonists such as tramadol [15].

“CIDP is a rare, but well-recognized, neurological complication of SLE”

Methadone is a μ -opioid agonist with efficacy greater than that of morphine. The unique properties related to the D-isomer include an enhancement of monoamine activity, and NMDA receptor antagonism. This might explain the efficacy of pain control when conventional opioid analgesics have failed [16,17]. Such bimodal action might explain the efficacy of pain control in the present case, given the failure of conventional opioid analgesics [11,16]. The dramatic response to methadone in this patient suggests central sensitization, where the NMDA receptor plays a major role in the pain processing.

Conclusion

In the uncommon combination of SLE with a CIDP with a chief complaint of pain, methadone appears to be an effective analgesic. Further study is warranted to confirm the exact mechanism of pain and its optimal management in such cases.

You can submit comments and questions on this article at:

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Disclosures

The authors have no relevant financial interests to disclose.

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Case study editor's comments:

This interesting case illustrates a number of difficulties in dealing with patients with neurological manifestations of SLE. Firstly, there is the difficulty in establishing the cause of neurological symptoms and therefore the prognosis, and whether there is any need for continued treatment. After the initial manifestation, the patient received acute treatment with IVIGs, but it is unclear whether some sort of maintenance treatment was prescribed. Secondly, as so often happens, compliance can be a great problem in SLE. This patient was put on maintenance treatment after renal involvement was diagnosed, but discontinued the medication at her own initiative. *Post aut propter*, a relapse of neurological symptoms occurred. Again, it is difficult to establish whether there was active inflammation or pre-existing damage. The lack of response to immunosuppressant treatment suggests the latter. This means that rather than treatment to reverse the process, treatment to ease the pain is now the remaining option (the third option of treatment of symptoms due to damage is always difficult or impossible). The choreography between the NMDA receptor, μ -opioids, and non- μ -opioids is still unclear and appears to be very complex. This case shows that choosing the right pain medication is an art in itself and best left to specialists.

Expert Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Tom Huizinga, MD, Peter Nigrovic, MD, Eric Ruderman, MD, and Hendrik Schulze-Koops, MD

GENETIC ASSOCIATION

Genetic association of the major histocompatibility complex with rheumatoid arthritis implicates two non-*DRB1* loci

Vignat C, Bansal AT, Balding DJ et al.
Arthritis Rheum 2009;**60**:53–62.

In addition to the shared epitope allele of the human leukocyte antigen-*DRB1* gene, other genes involved in antigen presentation may play a role in the pathogenesis of rheumatoid arthritis.

There is a great deal of research interest in the genetic basis of rheumatoid arthritis (RA), as this may ultimately lead to improved understanding of the pathophysiology of this disease, which in turn may result in better therapies. While the shared epitope (SE), a conserved sequence in the peptide-binding groove of the human leukocyte antigen-*DRB1* (*HLA-DRB1*) gene, is believed to be responsible for one-third of the genetic susceptibility to RA, other genes have been proposed to play a role, including the protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) gene, which may be a marker for the production of anti-cyclic citrullinated peptide (anti-CCP) antibodies.

In this study, the authors sought to identify major histocompatibility complex (MHC) genes, other than those at the *DRB1* locus, that may play a role in RA disease susceptibility. Using a case-control design, they genotyped the *HLA-DRB1* locus, along with 2360 single-nucleotide polymorphisms in the MHC region, in 855 RA patients and 977 controls. They identified 14 genes strongly associated with RA. Following logistic regression analysis and further investigation to eliminate genes in linkage disequilibrium with *DRB1*, they determined that two alleles, one of which (*0301) was found exclusively in anti-CCP-negative patients, remained strongly associated with RA. Their data indicate that

a reported disease association with the *HLA-DQA2* locus may, in fact, be a consequence of a previously unrecognized linkage disequilibrium with *DRB1*.

There is great interest in the role that antigen presentation, of either foreign antigens or altered self antigens, plays in the initiation and maintenance of the disease process in RA. This study provides additional evidence for the polygenic etiology of RA, and also points to two additional non-*DRB1* MHC genes that may be associated with it.

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Different patterns of associations with anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis in the extended major histocompatibility complex region

Ding B, Padyukov L, Lundström E et al.
Arthritis Rheum 2009;**60**:30–8.

Genetics can be used to identify risk factors for rheumatoid arthritis (RA). Ideally, risk factors can be used to provide a better description of diseases within the syndrome of RA, or to identify new pathways that can be used for drug development. In this large study, it was confirmed that human leukocyte antigen (HLA) is mainly a risk factor for anti-citrullinated protein antibody-positive RA. Moreover, it was found that both HLA-DR and HLA-DP are independent genetic risk factors for RA.

In two disease subsets of RA patients defined according to the presence or absence of anti-citrullinated protein antibodies (ACPA), 2221 single-nucleotide polymorphisms (SNPs) were genotyped from an area of approximately 10 Mb of the human

leukocyte antigen (HLA) region. Within the ACPA-positive group, about 300 SNPs reached locus-wide significance ($p < 2.3 \times 10^{-5}$) for ACPA-positive RA, whereas after adjustment for multiple testing, no SNPs reached significance for ACPA-negative RA.

This large analysis of >1900 cases and 2300 controls clearly showed that there are distinct genetic patterns of HLA associations in the two disease subsets of RA defined according to ACPA status.

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The DERA HLA-DR alleles in patients with early polyarthritis: protection against severe disease and lack of association with rheumatoid arthritis autoantibodies

Carrier N, Cossette P, Daniel C et al.
Arthritis Rheum 2009;**60**:698–707.

A subset of human leukocyte antigen-DR alleles has been proposed to encode a “rheumatoid arthritis-protective epitope”, which is a DERA amino acid sequence at positions 70–74 in the DRB1 molecule. In the present study, the association between DERA alleles and clinical outcome in patients with early polyarthritis (EPA) was investigated.

A total of 210 early polyarthritis (EPA) patients were evaluated in this prospective study over a period of 30 months. At the start of the study, >80% of the patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of rheumatoid arthritis (RA), 24.3% were positive for anti-Sa, 37.1% for anti-cyclic citrullinated peptide (CCP2), and 43.3% had immunoglobulin M-rheumatoid factor (IgM-RF) antibodies. The mean 28-joint count disease activity score (DAS28) of the patients was 5.28, and the modified-health assessment questionnaire score was >1 in 99 of the patients at baseline.

The number of patients with erosive disease increased during the 30-month follow-up, from 41 to 113 (score of ≥ 5 on the erosion component of the Sharp/van der Heijde Score [SHS]). The number of patients with severe erosive disease (score of ≥ 14 on the erosion component of the SHS) also increased, from 23 to 64. Despite rapid diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs), which effectively controlled disease activity in the majority of the patients (mean DAS28 decreased to 2.6 at 30 months), erosive damage occurred in 53.8% of the patients, with severe erosive disease developing in 37.1%.

The value of DERA alleles in the human leukocyte antigen-DRB1 molecule as a prognostic marker to evaluate the individual risk of reaching a preset severe disease outcome was examined firstly in univariate analyses, and secondly in a multivariate logistic regression analysis. DERA alleles were found in 62 patients. The presence of at least one DERA allele had a significant protective effect on the development of erosive disease (odds ratio [OR] 0.51; $p < 0.05$) and decreased the risk of evolving to severe disease at 30 months (OR 0.30; $p < 0.001$). However, DERA alleles did not protect patients who already had erosions at study inclusion. Furthermore, the mean numbers of joints with synovitis, the mean DAS28 scores, and the mean C-reactive protein (CRP) levels were not significantly different in DERA and non-DEA patients. Thus, the apparent protection conferred by the DERA alleles against severe disease was not associated with a clinically milder course of disease. No significant association of DERA with the production of any of the three RA-associated antibodies was observed. Finally, variables with a p value of less than 0.1 were included in a multiple logistic regression analysis to assess whether the presence of DERA alleles might serve as an independent prognostic marker at the first evaluation of the study patients. The results of this multivariate analysis were similar to those of the univariate analyses.

In conclusion, the presence of a DERA sequence in the DRB1 molecule contributed significantly to a better prognosis in this EPA cohort, but only in the absence of erosions at the start of the disease.

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The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee

MacGregor AJ, Li Q, Spector TD et al.
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The genetic influence on osteoarthritis (OA) at different anatomical sites of 992 individual twins, comprising 153 monozygotic and 343 dizygotic twin pairs, was analyzed by structural equation modeling in this investigation. Although showing a heritable component, OA at the hand, hip, and knee were not found to be determined by one general genetic factor.

Osteoarthritis (OA) can be described as the age-related degradation of joints at various body sites sharing common radiological and pathological features. Although twin and family as well as genetic linkage and association studies have shown a genetic contribution to the disease, it remains unclear

whether OA represents a single common phenotype. Therefore, the present study scored OA of the hand, hip, and knee from radiographs of 992 female twin volunteers (153 monozygotic and 343 dizygotic pairs) according to joint space narrowing, the presence of osteophytes, sclerosis, and cyst formation.

Firstly, scores were analyzed for the heritability of OA at the individual anatomical sites using structural equation modeling. Secondly, whether OA is influenced by shared genetic and environmental factors, and whether there exists a common genotype for OA across all body sites, was investigated using a multivariate analysis.

Considering all investigated anatomical sites separately, the presence of a genetic influence was confirmed for the hand distal interphalangeal (DIP), proximal interphalangeal (PIP), and carpometacarpal (CMC) joints, and for the hip and the knee. Regarding an overall genetic influence across the different anatomical sites, among the hand joints, the DIP and PIP joints were found to share genetic factors, with less genetic overlap found for the CMC joints. For the hand, hip, and knee OA, no genetic overlap was found to explain the co-occurrence of OA at these sites.

In conclusion, the present study indicates that the genetic influence on radiographic OA is joint-site specific. OA is unlikely to be determined by a single genetic factor and does not represent a single common phenotype.

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Genome-wide comparison between IL-17A- and IL-17F-induced effects in human rheumatoid arthritis synoviocytes

Zrioual S, Ecochard R, Tournadre A et al.
J Immunol 2009;**182**:3112–20.

In mouse models of arthritis, interleukin-17 (IL-17) plays a critical role in disease pathogenesis. The IL-17 family consists of multiple genes such as IL17A and IL17F. The present investigators showed that both IL-17A and IL-17F are specifically expressed in rheumatoid arthritis (RA) synovial tissue, but not in osteoarthritis synovial tissue. These results indicate that these two members of the IL-17 family may be involved in RA pathogenesis.

In this study, interleukin-17A (IL-17A) and IL-17F, two members of the IL-17 family, were detected in plasma cell-like cells from rheumatoid arthritis (RA) synovial tissue, but not in cells from osteoarthritis synovial tissue. Furthermore, in synoviocytes stimulated with either IL-17A or IL-17F, similar expression patterns were observed by microarray analysis. Both cytokines

also induced a similar expression pattern in the presence of tumor necrosis factor- α (TNF- α). Genes that were induced by IL-17A or IL-17F plus TNF- α were those that have previously been implicated in the pathogenesis of RA such as the chemokine receptor *CXCR4*, lipoprotein lipase (*LPL*), and *IL32*.

These data provide some circumstantial evidence that both IL-17A and IL-17F are implicated in the pathogenesis of RA.

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Specific association of type 1 diabetes mellitus with anti-cyclic citrullinated peptide-positive rheumatoid arthritis

Liao KP, Gunnarsson M, Källberg H et al.
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Type 1 diabetes mellitus is associated with anti-cyclic citrullinated peptide-positive rheumatoid arthritis, raising the possibility of a shared pathophysiological mechanism in the two diseases.

Autoimmune diseases, including type 1 diabetes and rheumatoid arthritis (RA), have been reported to occur concurrently with increased frequency, both in individuals and in families. In this study, the authors use population-based data to explore this association in a Swedish cohort. An incidence cohort of 1419 RA patients was compared with 1674 matched controls from the Swedish population registry. Sera from the RA patients were tested for rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and the protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) risk allele, which has been reported to be associated with both RA and type 1 diabetes mellitus. The diagnosis of diabetes mellitus was confirmed by questionnaire, telephone interview, and/or medical record review. The authors identified 25 subjects with type 1 diabetes mellitus and 88 subjects with type 2 diabetes mellitus.

Type 1 diabetes mellitus was associated with an increase in the risk of RA in this study (odds ratio [OR] 4.9). This association was specific for anti-CCP-positive RA (OR 7.3) and was not seen in anti-CCP-negative RA. Adjustment for the presence of the *PTPN22* risk allele attenuated the association with anti-CCP-positive RA (OR 5.3). There was no association found between type 2 diabetes mellitus and RA in this study. Stratifying the results by the presence or absence of RF found a similar association between RF positivity and type 1 diabetes mellitus.

The authors conclude that this study confirms the previously reported link between RA and diabetes, but note that this link is specific to anti-CCP- or RF-positive RA. They also suggest that the strength of the association with the *PTPN22* risk allele may

suggest the involvement of this gene in a common pathogenic mechanism for these two autoimmune diseases.

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INFECTIOUS COMPLICATIONS

Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents

Strangfeld A, Listing J, Herzer P et al.
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Herpes zoster develops more frequently during treatment with tumor necrosis factor (TNF) antagonists, and is statistically more common during treatment with anti-TNF monoclonal antibodies than with conventional disease-modifying antirheumatic drugs.

While there is wide recognition that the risk of bacterial infection is increased with the use of tumor necrosis factor (TNF) antagonists, there are few data on the risk of viral infections with these agents. In this study, the authors extracted data from the German Biologics Register (RABBIT) to assess the risk of herpes zoster episodes during treatment with TNF antagonists.

Patients were enrolled in this registry during the period from May 2001 to December 2006, and follow-up is planned through 2011; patients starting therapy with a biologic, plus a control group of patients switching conventional disease-modifying antirheumatic drugs (DMARDs), were asked to participate. All reported episodes of herpes zoster prior to November 2007 were included in the present analysis. During this time period, there were 86 episodes of zoster in 82 of the 5040 patients in the registry; 39 of these episodes occurred during treatment with an anti-TNF monoclonal antibody, 23 during treatment with etanercept, and 24 during treatment with conventional DMARDs.

The crude incidence rate of zoster was 11.1 per 1000 patient-years for the antibodies, 8.9 per 1000 patient-years for etanercept, and 5.6 per 1000 patient-years for conventional DMARD therapy. After adjusting for age, disease severity, and steroid use, the authors found that the risk of zoster was increased with TNF antibody therapy compared with conventional DMARD therapy (hazard ratio [HR] 1.82, 95% confidence interval [CI] 1.05–3.15). The risk was not significantly increased for etanercept therapy (HR 1.36, 95% CI 0.73–2.55) or for TNF antagonist therapy as a whole (HR 1.63, 95% CI 0.97–2.74).

In all, the results of this analysis suggest a modest increase in the risk of herpes zoster with the use of TNF antagonists, a risk that was statistically significant with the monoclonal antibodies but not with etanercept or the class as a whole. These data suggest that careful vigilance for the development of this complication during treatment with TNF antagonists is prudent. With the recent availability of a zoster vaccine, further research may be warranted to determine whether vaccination is appropriate prior to the initiation of these therapies.

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PROGNOSIS AND ASSESSMENT

Ultrasound colour Doppler measurements in a single joint as measure of disease activity in patients with rheumatoid arthritis – assessment of concurrent validity

Ellegaard K, Torp-Pedersen S, Terslev L et al.
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Color Doppler ultrasound of a single joint correlates with disease activity in rheumatoid arthritis, but more work is necessary to determine the role of this clinical tool.

Ultrasonography is increasingly used to define the extent of disease involvement in the joints of patients with rheumatoid arthritis (RA). With the addition of color Doppler, ultrasonography can be used to estimate blood flow in the synovial tissue, which is an indicator of inflammation and, thus, disease activity. Color Doppler flow has been shown to correlate with both serological and clinical measurements of disease activity.

In this study, the authors set out to determine whether color Doppler ultrasound (CDU) of a single active joint can be used to estimate overall disease activity. CDU was performed on the active wrists of 109 RA patients who were about to start therapy with a tumor necrosis factor antagonist (and thus presumed to have active disease). Blood flow measured by CDU in these patients showed significant correlation with 28-joint count disease activity score (DAS28), swollen joint counts, erythrocyte sedimentation rate, and C-reactive protein levels.

The authors concluded that CDU measurement of blood flow in a single joint could be used as a measurement of disease activity, although they acknowledge that further validation is required to determine whether this assessment is as accurate as one that evaluates multiple joints. They did not

evaluate the change in CDU in response to treatment, which would be important for establishing the clinical value of this measurement. These findings are also somewhat contradictory to recent work that has shown ultrasound activity despite clinical remission in RA [1]. While this study does provide interesting additional evidence for the utility of CDU in defining disease activity, more work is necessary to establish the optimal clinical role of this modality.

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American College of Rheumatology quality indicators for rheumatoid arthritis: benchmarking, variability, and opportunities to improve quality of care using the electronic health record

Adhikesavan LG, Newman ED, Diehl MP et al.
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Quality of care is aimed to meet a minimum standard in all institutions. In order to evaluate quality of care, quality indicators (QIs) have been developed. These are measures of process or outcome that are increasingly utilized to evaluate quality of care. In most hospitals, electronic data measurement systems will be in place to allow benchmarking. In one of the first large evaluations of QI in rheumatoid arthritis (RA), it was observed that the performance of rheumatologists in a large practice in Pennsylvania, USA, was excellent in RA treatment-related QIs but that the quality of RA monitoring measures was less optimal.

An electronic health record (EHR) review of >1000 rheumatoid arthritis (RA) patients seen during a 1-year period was performed by the present investigators. The aim of the review was to evaluate the American College of Rheumatology (ACR) quality indicator (QI) measures for RA and methotrexate drug monitoring. The percentage of individual QIs met in these patients was as follows:

- 94% for disease-modifying antirheumatic drug use.
- 85% for an intervention if RA worsened (if increased disease activity or progression of bony damage, change DMARD type, dose, or route; add a DMARD; or use oral or intraarticular glucocorticoids unless patient refuses or all of the above are contraindicated).

- 87% for the risks of methotrexate being discussed and documented.

However, the percentage QI met was clearly lower (69%) in the proportion of patients in which the ACR core set was measured. The ACR core set consists of joint examination, functional status, acute phase reactant levels, and physician and patient global assessments. Better QI performance was seen in rheumatologists with ≤10 years versus >10 years of experience for the ACR core set measurement (90% vs. 64%).

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Contemporary patterns of care and disease activity outcome in early rheumatoid arthritis: the ERAN cohort

Kiely P, Williams R, Walsh D et al.
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A considerable amount of data has shown that a shorter time period between symptom onset and initiation of disease-modifying antirheumatic drug (DMARD) treatment is associated with less disability and joint destruction. Nevertheless, in this large study from Europe of patients recruited between 2002 and 2007, it was shown that only a low proportion of patients received DMARDs within a relatively short time period (e.g. <3 months) from symptom onset. This study clearly demonstrates the need for rapid referral programs to improve patient outcomes.

There is significant evidence that a shorter time period between symptom onset and initiation of disease-modifying antirheumatic drug (DMARD) treatment is associated with less disability and joint destruction [1–3]. The present study investigated current treatment practices in terms of timing of treatment initiation.

A total of 808 patients with newly diagnosed rheumatoid arthritis (RA) were prospectively enrolled from 19 centers in the UK and Ireland. Standardized information was collected on case report forms at the first presentation, 3–6 months, 1 year, and annually thereafter. The choice and intensity of drug treatment was left to the discretion of individual centers. Overall, 62% of the patients fulfilled four or more American College of Rheumatology (ACR) criteria for RA at the first visit.

The median time from onset of symptoms to referral for secondary care, and to start the first DMARD, was 4 and 8 months, respectively. DMARDs were prescribed in 97% of the patients. The proportions of patients with a 28-joint count disease activity score (DAS28) >5.1 at baseline and 3 years

were 46% and 19%, respectively; DAS28 >3.2, 84% and 54%, respectively; and DAS28 <2.6, 6% and 33%, respectively.

These data indicate that current treatment practices are less than optimal both with regard to timing and intensity of treatment.

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Acute pediatric monoarticular arthritis: distinguishing lyme arthritis from other etiologies

Thompson A, Mannix R, Bachur R.
Pediatrics 2009;**12**:959–65.

Can Lyme arthritis be distinguished clinically from septic arthritis? These investigators reviewed cases of monoarthritis subject to arthrocentesis in a pediatric emergency department. While Lyme arthritis and septic arthritis exhibited marked differences, no decision rule could be established to clearly distinguish one from the other.

The differential diagnosis of acute monoarthritis in children varies from that in adults. Crystal arthropathy is extremely rare, while idiopathic inflammatory arthritis of childhood presents more commonly as monoarthritis than is the case in adults. However, in endemic areas, Lyme arthritis is an important consideration for both populations.

These investigators examined whether clinical and laboratory criteria could be found to distinguish between different etiologies among patients who underwent arthrocentesis in an academic, tertiary care, pediatric emergency department and who also (in the absence of positive bacterial cultures) had Lyme serology data available. Patients were classified as having septic, Lyme, or non-septic non-Lyme arthritis on the basis of final cultures and other laboratory tests. Clinical data were gathered by chart review. Of 179 children, 26% had septic arthritis, 31% had Lyme arthritis, and 43% had non-septic non-Lyme arthritis. Multiple differences achieving statistical significance were noted between these groups, but these differences were not clear-cut. In an attempt to develop a tool to distinguish septic from Lyme arthritis, the authors performed a multivariate logistic regression analysis comparing these two subgroups. Certain features were suggestive of Lyme disease (lack of fever, lower C-reactive protein levels,

history of tick bite, and lower joint white blood cell count), but these results could not be assembled into a decision rule with an acceptable ability to exclude sepsis. Even if such a rule had been identified, it is not clear that it could have been used in practice, where the key clinical distinction is between septic and non-septic arthritis, since more than half of the non-septic patients were excluded to develop the rule. Further limitations include the highly selected patient population and the quality of clinical examination data obtainable retrospectively (for example, among septic joints only 33% were “warm”, likely reflecting failure of documentation rather than actual absence of this finding, at least among joints amenable to examination). Therefore, while these authors provide interesting descriptive data, the results should not be regarded as proof that clinical judgment cannot help assess the relative probability of Lyme, septic, and non-septic arthritis in children. Of particular note was the finding that 40% of Lyme joints and 21% of non-septic non-Lyme joints were taken to the operating room for surgical irrigation, an intervention without utility in these diseases and a potential area for improvement in quality of care.

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The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort

Rudwaleit M, Haibel H, Baraliakos X et al.
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In the German Spondyloarthritis Inception Cohort (GESPIC), patients with early established ankylosing spondylitis (AS) and patients with non-radiographic axial spondyloarthritis (SpA) were directly compared. There was a high similarity between groups regarding clinical manifestations and levels of disease activity as well as an association between male sex and elevated C-reactive protein level with structural damage on radiographs.

Ankylosing spondylitis (AS) is the most frequent subtype of the spondylarthritides (SpA) that share several clinical manifestations and a genetic association with human leukocyte antigen-B27 (HLA-B27). The diagnosis of AS is normally based on radiographic changes in the sacroiliac (SI) joints, which are often slowly progressing and are thus one reason for the long diagnostic delay in AS. In early disease, active inflammation can be visualized by magnetic resonance imaging (MRI). Irrespective of the presence of radiographic changes, all cases of SpA with predominant axial involvement are considered to belong to one disease continuum called axial SpA.

The German Spondyloarthritis Inception Cohort (GESPIC) study group prospectively investigated the disease course of 462 patients with early axial SpA between September 2000 and December 2004. Patients having no radiographic changes in the SI joints but fulfilling the modified European Spondylarthropathy Study Group (ESSG) criteria and having a maximum disease duration of ≤ 5 years were classified as having non-radiographic axial SpA. A diagnosis of AS was based on radiographic findings and the fulfillment of modified New York criteria for AS and the restriction of disease duration to ≤ 10 years. The GESPIC patients had been treated according to the judgment of their local rheumatologists without any limitations. Assessments at study visits included evaluation on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), pain levels, life quality, peripheral arthritis, enthesitis, and uveitis. Spinal mobility was assessed using the Bath Ankylosing Spondylitis Metrology Index (BASMI), and laboratory tests included measurement of C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and HLA-B27 status. The authors compared patients with early axial SpA and patients with early AS with regard to predictors of outcome of disease and of radiographic changes.

At baseline, the mean symptom duration in AS patients ($n=236$) was 5.2 years compared with 2.6 years in SpA patients ($n=226$). AS patients were more frequently male compared with patients with SpA (64.0% vs. 42.9%; $p<0.001$). The frequency of HLA-B27 positivity; BASDAI score; mean level of pain; and disease activities of arthritis, enthesitis, and uveitis were similar in AS and SpA patients. Additionally, patients with AS were split into two subgroups according to their symptom duration (≤ 5 years vs. >5 years). The BASFI score was significantly better in SpA patients than in patients who had AS for ≤ 5 years ($p=0.027$), while CRP levels and ESR were significantly higher in AS patients. Multivariate logistic regression analysis revealed that both radiographic sacroiliitis as well as syndesmophytes were associated with elevated CRP levels and male sex, but not with HLA-B27 status, symptom duration, or BASDAI. HLA-B27 positivity was associated with a younger age at the onset of both AS and SpA.

This GESPIC study has allowed, for the first time, a direct comparison of patients with early established AS and patients with non-radiographic axial SpA, and has shown similarity between the two groups with respect to clinical manifestations and levels of disease activity. This supports the concept that both AS and SpA belong to the same disease continuum, irrespective of the presence of radiographic changes. Male sex and elevated CRP level were associated with structural damage observed on radiographs in early SpA, whereas the age at disease onset was determined by the HLA-B27 status of the patient.

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PATHOGENESIS

Therapeutic targeting of IL-6 trans signaling counteracts STAT3 control of experimental inflammatory arthritis

Nowell MA, Williams AS, Carty SA et al.
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The authors of this article investigated the role of interleukin-6 (IL-6) signaling pathways in inflammatory arthritis using murine models of antigen- and collagen-induced arthritis. Synovial fluid samples from patients with rheumatoid arthritis were also evaluated. They determined that IL-6-mediated signal transducer and activator of transcription 3 (STAT3) signaling plays a key role in lymphocyte trafficking and joint inflammation.

The importance of interleukin-6 (IL-6) in the onset, maintenance, and outcome of inflammatory diseases has been associated with the activation of the IL-6 receptor (IL-6R) subunit gp130, inducing the janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling cascade. Recently, the first humanized antibody against the membrane-bound and soluble form of IL-6R (tocilizumab) was approved for the treatment of patients with rheumatoid arthritis (RA).

The present authors examined the role of IL-6 in relapsing inflammatory events characteristic of chronic RA and investigated the efficacy of soluble gp130 (sgp130) in specifically blocking the soluble IL-6R signaling pathway (IL-6 trans signaling) – as a more sophisticated therapeutic target of autoimmune inflammation.

Antigen-induced arthritis was triggered in C57BL/6J mice by injection of 100 μ L methylated bovine serum albumin (mBSA) on days 0, 14, and 28. Knee diameters were measured daily and histological sections were analyzed by immunohistochemistry. Wildtype (WT) mice were compared with IL-6 knock-out, gp130 “knock-in” mice (gp130^{Y757F/Y757F}; in which intracellular signaling is disrupted and increased STAT3 activation occurs), and with knock-in mice crossed onto a heterozygous STAT3 background (gp130^{Y757F/Y757F}:STAT3^{+/-}). In further *in vivo* experiments, artificial sgp130 fusion protein was applied to DBA-1 mice in which collagen-induced arthritis (CIA) was elicited by an intradermal injection (challenge) of 100 μ L chicken collagen (21 days after immunization). To assess the importance of IL-6 trans signaling in humans, synovial fluid from patients with osteoarthritis (OA) and RA were analyzed by enzyme-linked immunosorbent assay (ELISA) and flow cytometry.

In accordance with previous observations, no signs of enhanced inflammation, progressive infiltration of leukocytes, or bone erosions were detected in IL-6 knock-out mice after

repeated mBSA challenge. In contrast, WT mice showed intensive pannus formation with elevated destruction of cartilage and significant enrichment of leukocytes, additionally reflected by high arthritis index scores. Immunohistochemical evidence of CD3⁺ T cells in WT joint sections associated with STAT3 and IL-17A expression strongly implicates a direct link between the presence of IL-6 and lymphocyte infiltration in inflamed tissue. Hyperactivation of STAT3 in gp130^{Y757F/Y757F} mice led to even greater numbers of IL-17-producing T cells and raised the severity of arthritis. However, no change in synovial infiltration was observed in gp130^{Y757F/Y757F}:STAT3^{+/-} mice suggesting a crucial role of gp130-mediated STAT3 signaling in T cell trafficking and retention in inflammatory arthritis.

In synovial fluids of patients with active RA, IL-6 and sIL-6R levels were significantly elevated, whereas, surprisingly, quantities of sgp130 (a natural antagonist of IL-6 trans signaling) were comparable in RA and OA patients. In addition, there were lower frequencies of CD4⁺IL-6R⁺ T cells in synovial fluid (in comparison with blood) and rapid depletion of membrane-bound IL-6R following activation with anti-CD3 and anti-CD28. These data indicate that IL-6 trans signaling is the predominant pathway in inflamed joints. Additionally, administration of the sgp130Fc fusion protein to mice with CIA (2.5 mg/kg every second day before the onset of CIA) resulted in reduced synovial hyperplasia, inflammatory infiltrates/exudates, and joint erosion, as well as halting further disease progression while vehicle control showed histological aggravation.

In conclusion, IL-6-mediated STAT3 signaling plays a major role in lymphocyte trafficking and sustained joint inflammation. Furthermore, IL-6 trans signaling may represent the specific pathway activated by IL-6, causing inflammatory arthritis. As sIL-6R is predominantly expressed in inflamed joints, specific therapeutic targeting of this with sgp130 might be an effective alternative to general IL-6R blockade, although this remains to be determined.

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Activation of the acquired immune response reduces coupled bone formation in response to a periodontal pathogen

Behl Y, Siqueira M, Ortiz J et al.
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Bone erosions occur due to uncoupling of osteoblast-mediated bone formation and osteoclast-mediated bone resorption. This uncoupling can lead to ankylosis in spondyloarthropathies and joint destruction in rheumatoid

arthritis. In this study in mice, it was demonstrated that activation of the acquired immune response enhances the uncoupling of the osteoclast/osteoblast axis by a mechanism involving activation of a transcription factor called FOXO1. This leads to the possibility that targeted interventions at this pathway may, in the future, be exploited to treat uncoupling effects in patients with rheumatic diseases.

In order to investigate how the acquired immune response could contribute to osteolytic lesions in rheumatic diseases, a pathogen was injected adjacent to bone in mice with or without prior immunization against the bacterium in this investigation.

Activation of the acquired immune response was found to increase osteoclastogenesis and decrease coupled bone formation. The latter was accompanied by an increase in nuclear translocation of the transcription factor FOXO1 *in vivo*, increased apoptosis of bone-lining cells, and a decrease in bone-lining cell density. A combination of *in vitro* experiments, which included both stimulation and inhibition of various inflammatory factors, indicated that reduction of the coupling of bone formation and resorption most likely occurs by the enhancement of bone-lining cell apoptosis through a mechanism that involves increased FOXO1 activation.

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A role of IgM antibodies in monosodium urate crystal formation and associated adjuvanticity

Kanevets U, Sharma K, Dresser K et al.
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Uric acid is commonly present in the plasma at levels above its solubility threshold, but clinical gout does not always occur. What factors induce crystal formation in some individuals but not others? In this report, the authors suggest that specific immunoglobulin M antibodies play an unexpected role in this process.

Recent advances in immunology have rescued gout from relative obscurity. Once regarded as an unfortunate byproduct of the loss of uricase during evolution, the formation of monosodium urate (MSU) crystals is now recognized as a “danger” signal that alerts the immune system to tissue injury. However, the formation of uric acid crystals *in vivo* is still not fully understood. Is it a completely passive process or regulated by immunological mechanisms? This group, led by an investigator who helped to identify the adjuvant activity of MSU crystals, examined whether antibodies might be involved. This hypothesis was motivated by

past observations that MSU crystals *in vivo* appear to be coated with antibodies, and that immunization of rabbits with certain crystals induces serum factors that promote precipitation of those crystals in a specific fashion.

To start their investigation, Kanevets et al. examined the efficacy of uric acid as an adjuvant in mice deficient in mature B cells (muMT) and found it to be impaired. Further implicating antibodies in this process, normal mice were found to exhibit substantial serological reactivity to MSU crystals at baseline, which could be “boosted” by immunization with MSU crystals. Hybridomas generated from these immunized mice yielded several hundred monoclonal antibodies, largely immunoglobulin M (IgM), capable of recognizing MSU but not other crystals. Some of these antibodies were found to promote crystallization of MSU from uric acid solutions *in vitro*, an activity that required the multivalency of IgM, since F(ab')₂ fragments could bind MSU crystals but were unable to induce their formation. To test whether this precipitation activity is relevant *in vivo*, the authors injected antibodies into mice. Injection tended to reduce serum uric acid levels in these animals and induce subtle inflammatory changes, suggestive of *in vivo* MSU precipitation. Furthermore, antibodies promoted the adjuvant activity of MSU crystals in muMT animals, although these data are less compelling.

Together, these findings are provocative and suggest that immune responses may in fact contribute to MSU crystal formation *in vivo*, but whether such responses are in fact operative in mice or humans remains to be determined.

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THERAPEUTICS RESEARCH

Prevention of cartilage degeneration in a rat model of osteoarthritis by intraarticular treatment with recombinant lubricin

Flannery CR, Zollner R, Corcoran C et al.
Arthritis Rheum 2009;**60**:840–7.

Lubricin is a large glycoprotein produced by chondrocytes and synovial fibroblasts that helps to reduce friction within the normal joint. Its production is reduced in the injured joint, potentially setting the stage for more injury. This group developed a recombinant lubricin analogue and showed that it reduces cartilage injury in a rat model of osteoarthritis.

Osteoarthritis (OA) is common, potentially debilitating, and relatively refractory to medical therapy. In OA, as well as in other injury and inflammation states, production of the joint lubricant lubricin decreases, potentially predisposing the joint to accelerated mechanical injury.

This industry-based group developed a shorter analogue of lubricin, LUB:1, for possible therapeutic use in OA. In this report, they describe the synthesis of LUB:1 and demonstrate that it adheres to the cartilage surface *in vitro* and *in vivo*, where it remains detectable upon the surface of rat cartilage for ≥28 days after a single injection. Testing this compound *in vitro*, they found that LUB:1 can reduce the coefficient of friction of cartilage and block the adherence of other cells. Finally, they show that repeated injection of LUB:1 into the knee of a rat that has been surgically injured to develop OA helps reduce cartilage wear. These results support the concept that lubricin replacement may one day become an important element of therapy for OA.

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Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial

Gottlieb A, Menter A, Mendelsohn A et al.
Lancet 2009;**373**:633–40.

Although disease-modifying antirheumatic drugs (DMARDs) and tumor necrosis factor (TNF)-blocking agents are effective in psoriatic arthritis (PsA), a substantial proportion of patients do not respond or have contraindications to these therapies, indicating a need for additional treatment options. Data from the present Phase II study demonstrate that treatment with ustekinumab is effective and safe in patients with PsA.

Psoriatic arthritis (PsA), a chronic, immune-mediated inflammatory joint disease, is prevalent in 7% to 34% of patients with psoriasis. Evidence suggests that interleukin-12 (IL-12) and IL-23 play an important role in the pathophysiology of PsA. Targeting the two molecules with ustekinumab, which is a monoclonal antibody that blocks the common p40 subunit of IL-12 and IL-23 and thus inhibits the binding of these cytokines to their receptor, seems to be an attractive approach to treatment.

In this double-blind, placebo-controlled, crossover trial, 146 patients with active PsA were randomized to either Group 1 (n=76), receiving ustekinumab 90 mg or 63 mg every week for 4 weeks (weeks 0–3) followed by placebo at weeks 12 and 16; or

Group 2, receiving placebo (weeks 0–3) followed by ustekinumab 63 mg at weeks 12 and 16 (n=70). The primary efficacy endpoint was a 20% improvement from baseline in American College of Rheumatology response criteria for RA (ACR20).

At week 12, significantly more patients in Group 1 compared with Group 2 achieved ACR20 (42% vs. 14%), ACR50 (25% vs. 7%), and ACR70 (11% vs. 0%) responses. Psoriasis measures were reduced with ustekinumab treatment; of the patients with psoriasis on $\geq 3\%$ body surface area, 52% in Group 1 and 5% in Group 2 had an improvement of $\geq 75\%$ in Psoriasis Area and Severity Index score at week 12 ($p < 0.0001$). Ustekinumab also improved baseline dactylitis and enthesopathy. At week 12, the two groups were similar with regard to adverse events (61% vs. 63%) and infections (36% vs. 30%). No serious adverse events were noted in Group 1 (three in Group 2).

In conclusion, the study shows ustekinumab to be efficacious and safe for the treatment of PsA, and provides clinical evidence of a role for the p40 subunit of IL-12/IL-23 in the pathophysiology of the disease. However, larger studies are needed to confirm the findings of this trial.

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Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis

Albers HM, Wessels JA, van der Straaten RJ et al.
Arthritis Rheum 2009;**61**:46–51.

What predicts the response to methotrexate therapy in children with juvenile idiopathic arthritis? These authors examined a retrospective series of 128 children treated with methotrexate and identified an association between a shorter lag time to initiation of therapy and an improved clinical response.

A key future goal in the practice of rheumatology is to be able to select appropriate therapy for our patients based on their presenting clinical, laboratory, and perhaps genetic features. To approach this issue with regard to the use of methotrexate among patients with juvenile idiopathic arthritis (JIA), these authors examined a retrospective database of 347 patients from several European countries. They identified 128 children in whom methotrexate was initiated and for whom follow-up clinical data as well as DNA samples were available. These children were divided into responders and non-responders, with response defined as any improvement in physician global assessment in the setting of stable or improved joint score, ranked on a novel scale of 1–5 by chart review. Responders and non-responders

were then compared by regression analysis to identify predictors of response, using defined clinical variables as well as genotype at six loci implicated in methotrexate metabolism. Compared with non-responders, responders were found to have the following:

- Higher initial disease activity.
- Lower initial methotrexate dose, explained by the use of higher initial doses in systemic JIA, which can be refractory to therapy.
- Shorter lag time between diagnosis and initiation of methotrexate (9.5 months vs. 16.3 months).

These data are intriguing, and are consistent with a clinical advantage of earlier initiation of methotrexate in JIA. However, a retrospective study such as this is prone to hidden confounders that might help explain why methotrexate was started earlier in some patients and not others. Given the multitude of hypotheses tested, and certain underlying assumptions (such as that it is meaningful to group all subtypes of JIA together), these results will require validation in other cohorts.

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Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis

van der Kooij SM, de Vries-Bouwstra JK,
Goekoop-Ruiterman YP et al.
Arthritis Rheum 2009;**61**:4–12.

While physician-measured parameters such as joint count are key measures of the efficacy of therapy for rheumatoid arthritis, improvement in patient quality of life is the ultimate goal. These authors analyzed patient-reported outcomes during the BeSt (Behandel-Strategieën) trial, and confirmed that combination therapy yielded more rapid improvement in these measures.

In the BeSt (Behandel-Strategieën) trial, >500 patients with rheumatoid arthritis (RA) were randomized between four treatment strategies:

- Sequential monotherapy (group 1).
- Step-up combination therapy (group 2).
- Initial combination therapy (methotrexate and sulfasalazine plus a steroid taper; group 3).
- Methotrexate and infliximab (group 4).

Data collected included patient-reported outcomes for physical and mental functioning as well as overall quality of life. In this article, the authors report the changes in these

parameters with therapy over time. While all groups improved, groups 3 and 4 (particularly group 4) improved fastest in terms of measures of physical function, pain, subjective disease activity, and global health. Clear differences in these parameters compared with monotherapy (groups 1 and 2) could be observed by 3 months. However, these differences disappeared by 2 years, by which time groups 1 and 2 had caught up. At the 2-year time-point, physical function in all groups remained below that expected in the Dutch population, although mental functioning had normalized.

These results can help inform the choice of initial therapy in patients with RA, leaving open for debate and investigation whether the accelerated improvement offered by aggressive initial therapy is worth the potential risks and definite costs.

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Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept

Borte S, Liebert UG, Borte M et al.
Rheumatology (Oxford) 2009;**48**:144–8.

Is vaccination safe and effective in patients with juvenile idiopathic arthritis (JIA) on immunosuppressants? This group examined vaccination for measles, mumps, and rubella in a small group of children with JIA and observed no toxicity or gross difference in efficacy.

Since the incidence of juvenile idiopathic arthritis (JIA) peaks in children aged <6 years, the question frequently arises whether the disease or its therapy affects the efficacy and safety of vaccination. In the absence of substantial data, pediatric rheumatologists frequently recommend avoiding live virus vaccination in these patients owing to concerns about the risk of infection in the face of uncertain response rates. To examine this issue, this group compared the outcomes of the measles, mumps, and rubella (MMR) vaccination in the following three groups of children with JIA (n=5 per group):

- Children placed on methotrexate following completion of both MMR vaccines.
- Children receiving MMR while on methotrexate alone.
- Children receiving MMR while on methotrexate and etanercept.

The efficacy of vaccination was assessed using anti-MMR antibody titers and enzyme-linked immunosorbent spot

(ELISPOT) assay to assess functional lymphocyte responses (interferon- γ production) in response to viral antigens. While variability was noted, there was no consistent impairment of anti-MMR responses in these patients as compared with age-matched controls. No toxicity was observed, and no disease flares appeared to result from vaccination. These results are reassuring, although it is clear that with such small sample sizes meaningful risks to patients could be easily missed.

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CARDIOVASCULAR RISK

Risk of venous thromboembolism with rheumatoid arthritis

Matta F, Singala R, Yaekoub AY et al.
Thromb Haemost 2009;**101**:134–8.

The authors of this study found that rheumatoid arthritis (RA) patients who do not undergo joint surgery have an increased risk of venous thromboembolism that may be controlled by antithrombotic prophylaxis. Such treatment therefore needs to be considered in patients with RA.

Abnormalities in coagulation factors have been detected in patients with rheumatoid arthritis (RA) and there is some evidence to suggest that RA patients have an increased incidence of thrombosis. The present authors therefore investigated the risk of pulmonary embolism (PE), deep vein thrombosis (DVT), and venous thromboembolism (VTE; defined as PE and/or DVT) in RA patients. Data on patients with RA and those without RA who were hospitalized in the US from 1979 to 2005 were obtained from the database of the National Hospital Discharge Survey (NHDS) and analyzed for orthopedic operation and PE and DVT incidence.

The analysis of the thromboembolism risk was performed separately for patients who did and did not undergo joint surgery. Among 5 718 000 RA patients and 922 606 000 patients without RA, 4 818 000 and 891 055 000, respectively, did not undergo joint surgery.

In the subgroup of patients who did not undergo joint surgery, PE incidence was 0.85% in those with RA compared with 0.38% in patients without RA with a relative risk (RR) for PE in RA patients of 2.25 (95% confidence interval [CI] 2.23–2.27). The RR for PE among these RA patients was higher in females than in males (2.56 [95% CI 2.54–2.59] vs. 1.70 [95% CI 1.67–1.74]) and was higher in African American than in Caucasian patients (3.75 [95% CI 3.64–3.85] vs. 2.08 [95% CI 2.06–2.10]). Overall, 1.64% of RA patients who did not have joint surgery had DVT

compared with 0.86% of non-RA patients who did not have a joint operation. Similarly to PE risk, the relative risk of DVT in these RA patients was almost two times higher compared with that of the patients without RA (1.90, 95% CI 1.89–1.92). Female and African American RA patients had an increased DVT risk versus male and Caucasian RA patients, respectively (2.02 [95% CI 2.01–2.04] in females vs. 1.66 [95% CI 1.64–1.69] in males, and 2.31 [95% CI 2.26–2.36] in African Americans vs. 1.73 [95% CI 1.72–1.75] in Caucasians). A slightly higher DVT risk was observed in younger (<50 years old) RA patients compared with those aged >50 years (1.94 [95% CI 1.89–2.00] vs. 1.34 [95% CI 1.33–1.34]). The incidence of VTE in RA patients who did not undergo joint surgery did not change from 1979 through 2005, with the risk of VTE in these patients being twice as high as in non-RA patients who did not undergo joint surgery (1.99, 95% CI 1.98–2.00).

Among patients who did undergo joint surgery, 0.67% of RA patients and 0.67% of non-RA patients had VTE. The VTE risk was not increased in the RA patients (RR 0.99, 95% CI 0.97–1.02), probably suggesting effectiveness of antithrombotic prophylaxis.

The authors conclude that RA is a risk factor for VTE and that antithrombotic prophylaxis may be considered to reduce VTE risk in RA patients.

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Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies

Tektonidou MG, Laskari K, Panagiotakos DB et al. *Arthritis Rheum* 2009;**61**:29–36.

The presence of antiphospholipid (aPL) antibodies in systemic lupus erythematosus patients is associated with thrombosis but prospective studies on the incidence of thrombosis, are lacking. In this prospective, case-control study it was observed that the thrombosis rate in aPL-positive patients was twice that in the aPL-negative patients; however, overall, the mean time to the first thrombosis event was about 7 years. The use of aspirin was associated with a protective effect in the aPL-positive patients, while the use of hydroxychloroquine had a protective role in both aPL-positive and aPL-negative patients.

A total of 144 systemic lupus erythematosus (SLE) patients who were positive for antiphospholipid (aPL) antibodies but without

previous thrombotic manifestations were compared with 144 age- and sex-matched SLE patients who were negative for aPL. The thrombosis rate was 29 per 144 aPL-positive patients (20%) and 11 per 144 aPL-negative patients (8%).

A multivariate analysis found significant predictors of thrombosis in aPL-positive patients to be male sex (hazard ratio [HR] 6.3), lupus anticoagulant (HR 3.5), and persistently positive anticardiolipin antibodies (HR 5.9). Male sex (HR 7.1) and hypertension (HR 6.5) were predictors of thrombosis in aPL-negative patients.

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Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies

Aviña-Zubieta JA, Choi HK, Sadatsafavi M et al. *Arthritis Rheum* 2008;**59**:1690–7.

This large meta-analysis of 24 studies confirms the reported increase in cardiovascular mortality rate in rheumatoid arthritis.

Rheumatoid arthritis (RA) has been associated with an overall increased mortality rate compared with the general population, and much of the premature mortality in RA is believed to be related to cardiovascular disease. However, estimates of cardiovascular mortality in RA have varied widely between investigations. In this meta-analysis, the authors reviewed published studies of cardiovascular mortality in RA through to July 2005. Studies were included in the analysis if they had a prespecified definition of RA, clearly defined cardiovascular outcomes, and reported standardized mortality rates (SMRs) as well as confidence intervals (CI).

Twenty-four studies met the defined criteria and were included in the meta-analysis; they included 111 758 RA patients and 22 927 cardiovascular events. Overall, the risk of cardiovascular death was increased by 50% (meta-SMR 1.50, 95% CI 1.39–1.61). The risk of death from ischemic heart disease was increased by 59% (meta-SMR 1.59, 95% CI 1.46–1.75), and the risk of death from cerebrovascular accident was increased by 52% (meta-SMR 1.52, 95% CI 1.40–1.67).

There was wide variability in the types of studies included in the meta-analysis. The only group that did not show an increased SMR for cardiovascular deaths were the inception cohort studies; however, these studies were small, with a pooled sample size of just 2175, which may not have been large enough to influence the overall results. Statistical analysis showed significant variability in the individual trial results,

suggesting that the cardiovascular SMR was not artificially increased by an absence of unpublished negative studies.

The studies included in this meta-analysis largely enrolled patients prior to the widespread use of biological agents for RA, so this manuscript provides an estimate of the SMR for cardiovascular events in the absence of these therapies. Recent data have suggested that the risk of cardiovascular death in patients treated with biological agents is closer to that of the general population. The estimated mortality risk provided by this meta-analysis could be useful as a comparator for the risk associated with these newer agents.

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Atherogenic serum lipid profile is an independent predictor for gouty flares in patients with gouty arthropathy

Mak A, Ho RC, Tan JY et al.

Rheumatology (Oxford) 2009;**48**:262–5.

A low serum level of high-density lipoprotein cholesterol, a component of atherogenic lipid profiles, was associated with gouty flares during 15 months of monitoring in a Singapore population.

The link between serum lipid profiles, atherosclerosis, and inflammation has become a subject of great interest for both

the clinical and research communities. Recent evidence has pointed to an association between atherogenic serum lipid profiles such as low serum high-density lipoprotein cholesterol (HDL-C), and inflammatory conditions such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS). In this study, the authors investigated whether such a lipid profile might be associated with flares of gouty arthritis.

Adult patients with a history of gout were followed for 15 months, and gouty flares (defined as rapidly developing transient arthritis or periarticular inflammation requiring additional therapy) were assessed and recorded. The study population had a mean serum urate level of 537 $\mu\text{mol/L}$. During follow-up, the authors recorded a mean of 7.4 attacks of gout in 100 patients.

There were several different parameters associated with gouty flares. However, in a multivariate analysis, only a longer duration of gout and lower mean fasting serum HDL-C remained as independent predictors of gouty flare.

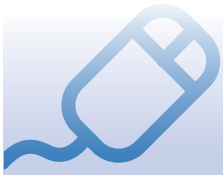
This study raises the intriguing possibility that low serum HDL-C levels may be associated with the inflammation in gout, as they have been in other inflammatory conditions. The very high serum urate levels in patients in this study casts some doubt on whether this relationship would hold in the face of more optimal hypouricemic therapy. In addition, nearly all of the patients in the study were ethnic Chinese or Malay; further investigation will be necessary to determine whether these results can be replicated in other ethnic populations.

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British Society for Rheumatology Annual Conference 2009

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The British Society for Rheumatology Annual Conference (BSR 2009) took place in Glasgow, UK, on 28th April–1st May 2009. There were a wide range of new data presented, and it would not be possible to summarize all of the content in this report. This review has therefore concentrated on the pathogenic and clinical aspects of rheumatoid arthritis (RA) that received the most interest.

Antibodies to citrullinated peptides

A number of interesting abstracts were related to the well-known association between RA and antibodies to citrullinated peptides (ACPA). Testing for the presence of antibodies to synthetic cyclic citrullinated peptides (CCP) is valuable in clinical practice, but the study of antibodies against naturally occurring citrullinated peptides, such as α -enolase or vimentin, may be of greater interest in understanding pathogenesis.

Development of ACPA appears to be the result of an interaction between inheritance of the *HLA-DRB1* shared epitope and smoking. Antibodies to citrullinated α -enolase (CEP-1) are of interest in RA since they are present in 40% of patients. Data from three RA cohorts were used to investigate the interaction of this antibody with known genetic factors and smoking [1]. Shared epitope-positivity was strongly associated with positivity to CEP-1, as opposed to positivity for citrullinated peptides in general. The odds ratio for this association was 53 for CEP-1⁺/CCP⁺ patients, compared with just 6 for CEP-1⁺/CCP⁻. There was a similar association for another RA susceptibility gene, protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*). These data suggest that CEP-1 may be of particular pathogenic interest. Data on antibodies to mutated citrullinated vimentin were also presented [2]. These antibodies are present in 80% of RA patients (of whom 99% are

anti-CCP2 positive) and associated with *HLA-DRB1*04* alleles. However, patients with antibodies to mutated citrullinated vimentin did not show any clinical difference in terms of erosions or nodules.

“Antibodies to citrullinated α -enolase (CEP-1) are present in 40% of RA patients”

New autoantigens were identified in 110 untreated RA patients by Western blot and matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometric analysis [3]. Two categories of antigens – enzymes of the glycolytic family and molecular chaperones – are also targeted by the autoantibody response in early RA. For some of these peptides, particularly far upstream element-binding proteins (FUSE-BP), citrullination seemed to be involved in antigenicity.

A study suggested a potential link between the pathogenesis of periodontitis and RA, both of which are associated with the shared epitope and smoking [4]. The major periodontal pathogen, *Porphyromonas gingivalis*, produces a peptidylarginine deiminase (PAD)-like enzyme, which may result in endogenous protein citrullination – a property apparently unique amongst oral pathogens. These citrullinated proteins were present in the inflammatory exudates in the gingival crevice and may therefore provide a substrate for the ACPA response in RA.

Tumor necrosis factor inhibitors and early arthritis

The early use of anti-tumor necrosis factor (anti-TNF) agents has previously been shown to result in high rates of long-lasting, and sometimes biologic/drug-free remission in the BeSt (Behandel Strategieën) study [5] and the study by Quinn et al. [6].

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Two other studies presented at BSR 2009 examined the use of other early anti-TNF regimens.

Long-term data from the PREMIER (A Multicenter, Randomized, Double-Blind Clinical Trial of Combination Therapy with Adalimumab plus Methotrexate versus Methotrexate Alone or Adalimumab Alone in Patients with Early, Aggressive RA who had not had Previous Methotrexate Treatment) study were presented [7]. This study randomized early RA patients to combination methotrexate and adalimumab or either agent alone. Previous data from the study have shown that there was greater radiographic inhibition in those who received combination therapy [8]. In an open-label extension, patients were switched to 3 years of adalimumab monotherapy after 2 years of blinded therapy. At the end of the initial 2 years, remission rates for groups that had received combination therapy, adalimumab monotherapy, and methotrexate monotherapy were 67%, 41%, and 39%, respectively; after an additional 3 years of adalimumab monotherapy, the respective rates were 60%, 52%, and 57%.

The NEO-RACo (Use of TNF-Blocking Therapy in Combination with Disease-Modifying Antirheumatic Drugs [DMARDs] in Patients with Early RA) study was a multicenter study that randomized patients to the combination therapy employed in the FIN-RACo (Finnish RA Combination Therapy) trial (methotrexate, sulphasalazine, hydroxychloroquine, and prednisolone targeted to achieve remission), together with either 6 months of infliximab or placebo [9]. At 6 months, 53% of patients receiving combination DMARD therapy alone were in remission according to American College of Rheumatology (ACR) criteria for RA, compared with 70% of those who received combination DMARD therapy with infliximab ($p=0.04$). Mean change in total Sharp score at 6 months was 1.4 in the placebo group and -0.2 in the infliximab group ($p=0.005$). Previous studies of anti-TNF agents in early arthritis evaluated infliximab in combination with methotrexate alone, compared with either methotrexate alone or a combination of DMARDs. This study demonstrates that addition of infliximab can add benefit over and above intensive combination DMARD therapy. Follow-up of the longer-term outcomes of this group in the future will be interesting.

The immunological factors that determine the possibility of long-lasting, biologic-free remission were investigated in patients who were in remission and stopping anti-TNF therapy [10]. Patients with RA have a reduction in the number of naïve T cells, a defect in the function of regulatory T cells, and an accumulation of abnormal pro-inflammatory inflammation-related cells (IRC). These subsets of cells were measured by six-color flow cytometry in patients in remission defined by Disease Activity Score cutoffs (DAS remission) for ≥ 6 months on anti-TNF before the therapy was withdrawn. The strongest predictor of sustained remission off-therapy was a short symptom duration (94% accuracy). Patients with sustained

remission also demonstrated normalization of T cell subsets before cessation of therapy, with significantly higher frequencies of naïve T cells ($p=0.002$) and lower IRC ($p=0.006$), suggesting recovery of thymic activity and control over inflammation-driven T cell differentiation. These data indicate that the possibility of drug-free remission after stopping anti-TNF is predictable and determined by achieving “immunological remission” in addition to clinical remission.

“Data from the BSR biologics registry show that disease duration prior to anti-TNF therapy remains high in routine clinical practice”

Three abstracts examined the impact of anti-TNF therapy in patients with moderate disease activity (28-joint count DAS [DAS28] 3.2–5.1). Data from the UK and Ireland Early RA Network were employed to examine the outcomes of patients with a (DAS28) >3.2 at 1 year after a further year of non-biological therapy [11]. Patients with a DAS28 not high enough to qualify for anti-TNF therapy in the UK (<5.1) after 1 year had poor outcomes after a second year of non-biological therapy, with only 25% achieving low disease activity and 22% needing to stop work. Of these patients, those with DAS28 4.2–5.1 performed worst, suggesting that this group may benefit from a change in guidelines to allow biological therapy. Data from the Yorkshire Early Arthritis Register showed that 33.3% of patients with a DAS28 3.2–5.1 after 6 months of escalating DMARD therapy deteriorated functionally over a further 6 months of DMARD therapy, compared with 23.4% of patients with DAS28 <3.2 and 41.5% of patients with DAS28 >5.1 [12]. Data from the BSR biologics registry showed that patients with established RA and a baseline DAS28 3.2–5.1 had a similar benefit from anti-TNF to those with DAS28 >5.1 as measured by the Health Assessment Questionnaire [13].

However, data from the BSR biologics registry also show that, although shortening compared with 2001, disease duration prior to anti-TNF therapy remains high in routine clinical practice [14]. The median disease duration prior to anti-TNF therapy was 12 years in 2001/2002 and 9 years in 2007. There was a small reduction in baseline DAS28 over the same time-period, from 6.8 to 6.4, and a small increase in remission rate, from 9% to 12%.

B cell therapies

A number of abstracts examined the effects of repeat cycles of B cell depletion using rituximab in terms of changes in efficacy and safety on subsequent cycles.

Short-term safety data for rituximab, as shown in the REFLEX (Randomized Evaluation of Long-Term Efficacy

of Rituximab) and DANCER (Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA) licensing trials, was good with only a modest increase in serious infection rate that was comparable to other immunosuppressive therapies [15,16]. The reason for such a favorable risk–benefit profile is believed to be due to the sparing of CD20-negative plasma cells that are responsible for maintaining normal immunoglobulin levels. Therefore, an important question is whether long-term suppression of B cells would result in a progressive attrition of plasma cells and hypogammaglobulinemia. Six-year safety data from pooled clinical trials of rituximab (involving a total of 2578 patients) were presented [17]. These data generally appear reassuring with no increase in serious infection rate after four cycles of therapy, and a small increase (with wide confidence intervals) in the limited number of patients receiving five cycles.

Efficacy data from the long-term follow up of 179 patients in the REFLEX trial who had received at least three cycles of rituximab were also presented [18]. Efficacy appears to be maintained, with an increase in remission rate from 8.8% in cycle 1 to 17.6% in cycle 2. However, a response in cycle 1 was required to qualify for retreatment and later results may have been subject to a selection bias for better responders to remain in follow-up.

“6-year safety data from pooled clinical trials of rituximab appear reassuring”

One study also assessed the responses to repeat cycles of rituximab in patients who had failed to respond to their first cycle of rituximab retreatment [19]. A total of 25 non-responders to a first cycle of rituximab (from an overall group of 104 responders and non-responders) were retreated with a second cycle 6 months after the first. Highly sensitive flow cytometry was used to measure the very small numbers of B cells that persist after rituximab therapy. In the first cycle of therapy, 90% of clinical non-responders had incomplete B cell depletion, which was predicted by higher numbers of circulating memory B and preplasma cells at baseline. Retreatment with a second cycle of rituximab enhanced B cell depletion and enhanced the clinical response rate, with 72% of patients who had initially failed to respond to rituximab achieving a response according to European League Against Rheumatism (EULAR) criteria for RA.

An alternative approach in patients who initially fail to respond to rituximab is to switch to a different biological agent. However, there are limited data on the safety of blockade of additional immunological pathways in patients in whom B cells are already below normal numbers. Data from the long-term follow-up of the 2578 patients from pooled rituximab clinical trials attempted to address this issue [20]. Of these 2578 patients, 185 withdrew and received a different biological

agent (150 TNF inhibitors, 25 abatacept, and 10 anakinra or experimental biologics). No increase in serious infection rate was noted (the rate was 6.99 per 100 patient-years before another biological agent and 5.49 per 100 patient-years after the alternate agent); however, these data are based on just 10 serious infections in 182 patient-years, so further follow-up is needed to ensure the safety of this approach.

New biologics

There were a large number of abstracts relating to three new biological agents that have reached Phase III clinical trials: the new anti-TNF agents, golimumab and certolizumab, and the interleukin-6 (IL-6) inhibitor, tocilizumab.

Both new anti-TNF agents aim to improve short- and long-term efficacy by pharmacokinetic factors, in particular the avoidance of immunogenicity. Golimumab is a humanized form of infliximab and certolizumab is a PEGylated Fc-free anti-TNF agent. Whilst many abstracts have shown that these agents have similar efficacy and safety to the existing three licensed anti-TNF agents, longer term outcomes or head-to-head switching trials would be required to confirm any genuine advantage.

Golimumab demonstrated similar efficacy and safety to existing anti-TNF agents at 6 months in methotrexate inadequate responders [21–23]. In patients that discontinued another anti-TNF agent for any reason and were switched to golimumab, EULAR response rates were 58.5%, 49%, and 27.1% at 3 months for golimumab 100 mg, golimumab 50 mg, and placebo, respectively (with any DMARD or corticosteroid taken at baseline continued) [24]. Six-month results were similar. A trial that compared four different combinations of golimumab/placebo and methotrexate/placebo failed to meet its primary endpoint of ACR50 in patients receiving golimumab (50 mg or 100 mg) plus methotrexate combination therapy compared with either agent alone ($p=0.053$), but a modified *post hoc* comparison yielded a p value of 0.049 [25].

“Golimumab demonstrated similar efficacy and safety to existing anti-TNF agents at 6 months in methotrexate inadequate responders”

Certolizumab plus methotrexate demonstrated retardation of radiographic erosion at 6 months compared with methotrexate alone [26], improved productivity at 6 months [27], and improved pain and quality of life at 52 weeks [28] in methotrexate inadequate-responders. One study suggested good longer term efficacy [29]. Patients completing 1 year of randomized therapy in the RAPID I (RA Prevention of Structural Damage I) trial could enter a long-term extension

and 2-year data were presented. The response rate seemed stable, with ACR20/50/70 responses of 82%, 58%, and 30%, respectively, at the end of year 1; and 79%, 54%, and 35%, respectively, at the end of year 2 for patients who were treated with 400 mg certolizumab throughout. However, as with all long-term extension studies there may be a bias for retention of better responders. Of the 265 patients who entered the long-term extension, 237 (89%) completed 2 years of follow-up and were analyzed.

There were a very large number of abstracts concerning tocilizumab. In general, safety and efficacy is comparable to, or possibly in some situations better than, existing biologics. Of particular interest, the DAS28 response appears to be as good regardless of the number of anti-TNF agents previously failed [30], and, unlike many other biologics, it appears superior to methotrexate in suppressing disease activity when used as monotherapy in early RA [31]. These data suggest that the determinants of best responses to tocilizumab may be different from those usually seen in anti-TNF trials (e.g. early initiation and requirement for methotrexate) and future mechanistic studies using this agent will be interesting.

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Disclosures

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Important Treatment Considerations

Indications

Rheumatoid arthritis
HUMIRA in combination with methotrexate, is indicated for:
■ the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
■ the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.
HUMIRA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
HUMIRA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.


Polyarticular juvenile idiopathic arthritis
HUMIRA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in adolescents aged 13 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). HUMIRA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Psoriatic arthritis
HUMIRA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. HUMIRA has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Ankylosing spondylitis
HUMIRA is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Crohn's disease
HUMIRA is indicated for treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. For induction treatment, HUMIRA should be given in combination with corticosteroids. HUMIRA can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate.

Psoriasis
HUMIRA is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.



Posology and method of administration
HUMIRA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or psoriasis. Patients treated with HUMIRA should be given the special alert card.
After proper training in injection technique, patients may self-inject with HUMIRA if their physician determines that it is appropriate and with medical follow-up as necessary.
During treatment with HUMIRA, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Dose Interruption
Available data suggest that re-introduction of HUMIRA after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption.

Adults
Rheumatoid Arthritis
The recommended dose of HUMIRA for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.
Methotrexate should be continued during treatment with HUMIRA.
Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with HUMIRA.
In monotherapy, some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg adalimumab every week.
Psoriatic arthritis and ankylosing spondylitis
The recommended dose of HUMIRA for patients with psoriatic arthritis or ankylosing spondylitis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.
For all of the above indications, available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Crohn's disease
The recommended HUMIRA induction dose regimen for adult patients with severe Crohn's disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at week 2, can be used with the awareness that the risk for adverse events is higher during induction.
After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped HUMIRA and signs and symptoms of disease recur, HUMIRA may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.
During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.
Some patients who experience decrease in their response may benefit from an increase in dose intensity to 40 mg HUMIRA every week.
Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Psoriasis
The recommended dose of HUMIRA for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.
Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Elderly patients
No dose adjustment is required.

Children and adolescents
Polyarticular Juvenile Idiopathic Arthritis
The recommended dose of HUMIRA for patients with polyarticular juvenile idiopathic arthritis, aged 13 years and above is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.
Available data suggest that clinical response is usually achieved within 12 weeks of treatment.
Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Impaired renal and/or hepatic function
HUMIRA has not been studied in these patient populations. No dose recommendations can be made.

Contraindications
HUMIRA is contraindicated in patients with active tuberculosis or other severe infections such as sepsis, and opportunistic infections; moderate to severe heart failure (NYHA class III/IV) and those with hypersensitivity to adalimumab or any of the excipients.

Warnings and Precautions
Patients taking TNF-blockers are more susceptible to serious infections.
Patients must therefore be monitored closely for infections including tuberculosis before, during and after treatment with HUMIRA. Monitoring for infections should be continued for five months following treatment.
HUMIRA should not be initiated in patients with active infections until infections are controlled.
In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with HUMIRA should be considered prior to initiating therapy.
If new infections develop during treatment, patients should be monitored closely and undergo a complete diagnostic evaluation. If a new serious infection or sepsis develops HUMIRA should be discontinued and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Caution should be exercised when considering the use of HUMIRA in patients with a history of recurring infection or underlying conditions, which may predispose patients to infections, including the use of concomitant immunosuppressive medications.
Serious infections, including sepsis, due to bacterial mycobacterial, invasive fungal, viral or other opportunistic infections have been reported with HUMIRA.
Hospitalisation or fatal outcomes associated with infections have been reported.
Before initiation of therapy with HUMIRA, patients must be evaluated for active or inactive (latent) tuberculosis. This evaluation should include

a detailed medical history with a personal history of tuberculosis or possible previous exposure to patients with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient's alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, HUMIRA therapy must not be initiated.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is diagnosed, appropriate treatment for latent tuberculosis must be initiated with anti-tuberculosis prophylaxis therapy before starting treatment with HUMIRA, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should also be considered before the initiation of HUMIRA.

Use of anti-tuberculosis therapy should also be considered before the initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with HUMIRA.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection occur during or after therapy with HUMIRA.

Other opportunistic infections, including invasive fungal infections have been observed in patients receiving HUMIRA. These infections have not consistently been recognised in patients taking TNF-blockers and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

HUMIRA has been associated, in rare cases, with new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease including multiple sclerosis, Guillain-Barré syndrome and optic neuritis. Caution should be exercised when considering HUMIRA in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including HUMIRA, who are chronic carriers of this virus. Some cases have had fatal outcome. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating HUMIRA therapy. Carriers for HBV who require treatment with HUMIRA should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Serious allergic reactions have not been reported with subcutaneous administration in clinical trials. Non-serious allergic reactions associated with HUMIRA were uncommon during clinical trials. In postmarketing, serious allergic reactions including anaphylaxis have been reported very rarely. If an anaphylactic reaction or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy initiated.

The needle cover of the syringe contains natural rubber (latex). This may cause severe allergic reactions in patients sensitive to latex.

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. The occurrence was rare. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients. A possible risk of malignancy including lymphoma in patients treated with TNF antagonists cannot be excluded. Caution should be exercised in considering HUMIRA treatment of patients with a history of malignancy.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with HUMIRA have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for Crohn's disease. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with HUMIRA cannot be excluded.

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with HUMIRA.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-blocking agents. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. All patients should be advised to seek immediate medical attention if develop signs and symptoms suggestive of blood dyscrasias while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant haematologic abnormalities.

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA. It is recommended that polyarticular juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating HUMIRA therapy.

Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving HUMIRA. HUMIRA should not be used with caution in patients with mild heart failure (NYHA class I/II). HUMIRA must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

HUMIRA may result in the formation of autoimmune antibodies. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA and is positive for antibodies against double-stranded DNA, further treatment with HUMIRA should not be given.

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Therefore, the combination of adalimumab and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of HUMIRA and abatacept is not recommended.

There is limited safety experience of surgical procedures in patients treated with HUMIRA. The long half-life of HUMIRA should be taken into consideration when a surgical procedure is planned, and the patient should be monitored for infections.

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that HUMIRA does not worsen or cause strictures.

Interactions
HUMIRA has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking HUMIRA as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when HUMIRA was given together with methotrexate in comparison with use as monotherapy. Administration of HUMIRA without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab.
The combination of HUMIRA and anakinra is not recommended.
The combination of HUMIRA and abatacept is not recommended.

Pregnancy and lactation
Administration of adalimumab is not recommended during pregnancy. Women of childbearing potential should use adequate contraception and continue its use for at least five months after the last HUMIRA treatment. Women must not breast-feed for at least five months after the last HUMIRA treatment.

Adverse drug reactions
Very common ≥1/10; *Injection site reaction.* *Common* ≥1/100 <1/10; *Lower respiratory infections, viral infections, candidiasis, bacterial infections, upper respiratory infections, dizziness, headache, neurologic sensation disorders, cough, nasopharyngeal pain, diarrhoea, abdominal pain, stomatitis and mouth ulceration, nausea, hepatic enzymes increased, rash, pruritus, musculoskeletal pain, pyrexia, fatigue. Uncommon* ≥1/1,000 <1/100; *opportunistic infections, sepsis, abscess, joint infection, skin infection, superficial fungal infection, skin papilloma, neutropenia, leucopenia, thrombocytopaenia, anaemia, lymphadenopathy, leucocytosis, lymphopaenia, systemic lupus erythematosus, angioedema, drug hypersensitivity, hypokalaemia, lipids increased, appetite disorders, hyperuricaemia, mood disorders, anxiety, syncope, migraine, tremor, sleep disturbance, vision disorders, ocular sensation disorders, infection, irritation or inflammation of the eye, ear discomfort, arrhythmias, tachycardia, hypertension, flushing, haematoma, asthma, dyspnoea, dysphonia, nasal congestion, rectal haemorrhage, vomiting, dyspepsia, abdominal bloating, constipation, urticaria, psoriasis, ecchymosis and increased bruising, purpura, dermatitis and eczema, hair loss, haematuria, renal impairment, bladder and urethral symptoms, menstrual cycle and uterine bleeding disorders, chest pain, oedema, influenza like illness, blood creatine phosphokinase increase, activated partial thromboplastin time prolonged, autoantibodies present, accidental injury, impaired healing.* *Rare* ≥1/10,000 <1/1,000; *necrotising fasciitis, viral meningitis, diverticulitis, wound infection, lymphoma, solid organ tumours, malignant melanoma, squamous cell carcinoma of the skin, pancytopenia, idiopathic thrombocytopaenia purpura, serum sickness, seasonal allergy, thyroid disorder, hypercalcaemia, hypocalcaemia, multiple sclerosis, facial palsy, panophthalmitis, iritis, glaucoma, hearing loss, tinnitus, cardiac arrest, coronary artery insufficiency, angina pectoris, pericardial effusion, congestive cardiac failure, palpitations, valvular occlusion, aortic stenosis, thrombophlebitis, aortic aneurysm, pulmonary oedema, pharyngeal oedema, pleural effusion, pleurisy, pancreatitis, intestinal stenosis, colitis, enteritis, oesophagitis, gastritis, hepatic necrosis, hepatitis, hepatic steatosis, cholelithiasis, blood bilirubin increased, erythema multiforme, panniculitis, rhabdomyolysis, proteinuria, renal pain.*

Additional adverse drug reactions reported post-marketing
Intestinal perforation, reactivation of hepatitis B, demyelinating disorders including optic neuritis and Guillain-Barré syndrome, interstitial lung disease including pulmonary fibrosis, cutaneous vasculitis, anaphylaxis, hepatosplenic T-cell lymphoma.

Overdose
Multiple intravenous doses of 10mg/kg have been administered without observation of dose limiting toxic effects.

References: 1. Breedveld FC, Weisman MH, Kavanaugh AF, et al, for the PREMIER Investigators. The PREMIER Study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54:26-37. 2. Keystone EC, Kavanaugh AF, Sharp JT, et al. Inhibition of radiographic progression in patients with long-standing rheumatoid arthritis treated with adalimumab plus methotrexate for 5 years. Presented at: European League Against Rheumatism Annual Scientific Meeting; June 2007; Barcelona, Spain.

HUMIRA
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A Promise for Life



We danced

We dance

We will dance

Radiographic results for today and for tomorrow

Early, aggressive rheumatoid arthritis (RA)

- **61%** of HUMIRA + MTX-treated patients had no radiographic progression (change in TSS ≤ 0.5 from baseline) at 2 years vs 34% of MTX-treated patients ($P < 0.01$) (PREMIER)¹

Long-standing RA

- In the DE019 open-label extension, **58%** (66/113) of patients remaining from the original HUMIRA 40 mg eow + MTX group had no radiographic progression (change in TSS ≤ 0.5 from baseline) at year 5 vs 40% (34/86) of patients initially receiving placebo + MTX²

Treat Today for Tomorrow in RA

HUMIRA
adalimumab

HUMIRA is indicated for the treatment of RA, AS, PsA, Ps, CD, and JIA. See abbreviated SmPC on the adjacent page for more information.

PREMIER was a 2-year, multicentre, randomised, double-blind study (N=799) evaluating the safety and efficacy of HUMIRA 40 mg SC eow in subjects with moderate-to-severe early (less than 3 years' duration) rheumatoid arthritis who were methotrexate (MTX)-naïve. Patients were randomised to receive HUMIRA + MTX, HUMIRA, or MTX. The primary efficacy endpoints included ACR50 response and change in modified TSS at Week 52 in patients receiving HUMIRA + MTX vs MTX alone. Patients treated with HUMIRA + MTX had a mean change in TSS of 1.3 at 52 weeks compared with 5.7 for patients treated with MTX ($P < 0.001$).

DE019 was a 1-year, randomised, double-blind, placebo-controlled study (N=619) in which patients received MTX plus either HUMIRA 40 mg eow, HUMIRA 20 mg weekly, or placebo. Primary endpoints were ACR20 at 24 weeks and change in modified TSS and HAQ DI at 52 weeks for HUMIRA 40 mg eow + MTX vs placebo + MTX. Patients taking HUMIRA 40 mg + MTX had a mean change in TSS of 0.1 at 1 year vs 2.7 for patients taking placebo + MTX ($P \leq 0.001$). Patients who completed the double-blind phase were eligible to enroll in the 4-year OLE study to receive HUMIRA 40 mg eow plus MTX. At 5 years, 304 patients had completed the study. Radiographs were taken and assessed for TSS at baseline and at 1, 3, and 5 years.

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