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Pharmacogenetics of Tumor Necrosis Factor Antagonists in Rheumatoid Arthritis: An Update

Hamid Bashir, MD, and Prabha Ranganathan, MD
Department of Medicine, Washington University School of Medicine, St Louis, MO, USA

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease of unknown etiology that is associated with progressive disability and an increased mortality rate. The primary site of pathology is the synovium of the joints, which becomes inflamed and proliferates to form a pannus [1]. Many cell populations, including monocytes, macrophages, B cells, T cells, endothelial cells, and fibroblasts, participate in the ongoing inflammatory process [2]. B cell–T cell interactions are integral to the inflammatory process in RA; B cells may function as antigen presenting cells and provide important co-stimulatory signals required for CD4+ T cell clonal expansion and effector functions [3,4]. RA is thought to be initiated by T lymphocytes recognizing antigens in the synovial tissue. Activated T cells, macrophages, and fibroblasts produce pro-inflammatory cytokines that play a key role in the synovitis and tissue destruction in RA. Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) are the two major pro-inflammatory cytokines that enhance synovial proliferation and stimulate secretion of other inflammatory cytokines, matrix-degrading metalloproteinases, adhesion molecules, and prostaglandin E2 – all of which are instrumental in tissue destruction in RA [5]. Recognition of the crucial roles of these cytokines in inflammation in RA has led to the development of targeted biological therapies, such as agents that block the action of TNF-α. These biological treatments have revolutionized the treatment of RA. Randomized clinical trials have shown that these agents yield significant clinical benefit in patients with inadequate responses to other disease-modifying drugs [6,7].

Despite the widespread use of these novel therapeutic regimens, only 50–70% of patients receiving anti-TNF therapy achieve at least an ACR20 response during clinical trials, suggesting that there remains a significant proportion of patients that does not respond [8]. As these drugs are expensive and have the potential to cause serious toxicity [9–12], identifying patients most likely to respond favorably is desirable. There has been a growing interest in recent years in pharmacogenetic approaches to identifying such patients. These approaches are particularly relevant in RA where long-term therapy is required and several therapeutic options exist without a universal drug of choice.

Inherited differences in drug effects and drug metabolism were first documented in the 1950s [13,14]. These concepts evolved into a field of research called “pharmacogenomics”, which focuses on the interactions between genetic variations and drug effects in individuals. Pharmacogenetics has been rediscovered by a broader spectrum of academia and industry, creating the term “pharmacogenomics”. This term applies to genome-wide approaches (rather than single or multiple genes

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of interest) that are used to identify genetic variations that govern response to medications [15]. Unlike other factors that influence drug response, inherited determinants offer the advantage of remaining stable throughout a person’s lifetime [16]. Inter-individual differences in drug response may be caused by common genetic variations (called polymorphisms) in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets. These genetic variants of interest come in many forms; single nucleotide polymorphisms (SNPs) are the most common, with possibly 15 million in the human genome. SNPs are caused by a difference in one base-pair in the DNA sequence, which may result in a change in the function or quantity of the transcribed protein depending on the nucleotide change and the location [15]. There are >30 families of drug-metabolizing enzymes in humans, and essentially all are encoded by genes with genetic variants, many of which translate into functional changes in the proteins encoded [16].

**TNF blockers in RA**

TNF-α belongs to a family of proteins important in immune regulation and programmed cell death. It has a key role in the inflammatory process in RA and is expressed by many cells within the immune system. TNF-α is involved in stimulating cytokine (including its own) production, in enhancing the expression of adhesion molecules, and in neutrophil activation; it is also a costimulator of T cell activation and antibody production by B cells [17–19]. It induces an array of biological responses in innate as well as adaptive immunity by binding to one of two receptors: TNF-RI (subsequently referred to as the p55 TNF receptor) and TNF-R1I (the p75 TNF receptor). These receptors are expressed on nearly all human cells [20].

Three anti-TNF agents (TNF blockers) are currently approved for use in the treatment of RA. Etanercept is a fusion protein consisting of two p75 TNF receptors linked to the Fc portion of human immunoglobulin G1 (IgG1). This agent binds to soluble TNF-α and lymphotoxin-α (LT-α), thereby preventing binding of these molecules to their cell-surface receptors. However, etanercept does not bind to transmembrane TNF-α or induce lysis of target cells. Besides etanercept, two monoclonal antibodies against TNF-α are available: the chimeric antibody infliximab, and the fully humanized antibody adalimumab. These two monoclonal antibodies directly bind TNF-α on the cell surface, fix complement, and induce lysis of the target cells [21–23].

**Pharmacogenetic studies of TNF blockers in RA**

Pharmacogenetic studies of anti-TNF therapies in RA have involved the obvious candidate gene, TNF, coding for TNF-α, and the genes encoding TNF-α receptors. In recent years, polymorphisms in genes encoding proteins related to TNF-α have been identified that may be associated with treatment outcomes in RA [24–26]. Several SNPs have been described in the TNF locus (Fig. 1), both within the TNF gene itself and in proximity to it [27,28]. Among these, SNP –308 A/G in the promoter region of TNF has been the most widely studied for its effects on treatment responses to TNF blockers in RA patients. This polymorphism may influence the binding of transcription factors and control TNF production after lipopolysaccharide (LPS) stimulation [25,29,30]. Another promoter SNP, TNF –857 C/T, may directly affect the transcription efficiency of the TNF gene [24] although its effects on cellular levels of TNF remain controversial [31,32].

Another category of polymorphisms described in the TNF locus are the DNA microsatellites, which are highly polymorphic and serve as genetic markers. Microsatellites are repeat sequences of the bases A and T found in the intronic portions of DNA. Although they are not transcribed into mature mRNA, they can alter DNA folding and conformation and hence the transcription of various enzymes and proteins. The TNF locus has five such microsatellites, TNFα–e, further designated based on the number of repeat sequences [33]. Genetic polymorphisms have also been described for other cytokines and their receptors, such as IL-1, IL-10, and the Fc gamma (Fcγ) receptor. For example, the gene encoding the IL-1 receptor antagonist (IL-1ra), IL1RN, has a variable allelic polymorphism. The IL1RN*2 allele has been described as a factor determining severity in several autoimmune diseases and has paradoxically been associated with increased production of IL-1ra by monocytes in vitro [34]. The Fcγ receptor found on the surface of cells in the immune system binds the Fc portion of an Ig molecule and affects several cell-specific functions, such as phagocytosis, degranulation, antibody dependent cell-mediated cytotoxicity, cytokine release, and regulation of antibody production [35]. Fcγ receptor polymorphisms may alter Fcγ receptor function by enhancing or diminishing its affinity for IgGs [36]. The most frequent polymorphism of Fcγ receptor IIIA, a subclass of Fc receptor, is a point mutation affecting amino acids in codon 158 in the extracellular domain [37].

**TNF promoter polymorphisms**

Fonseca et al. demonstrated that RA patients with the –308 G/G genotype had a better response to infliximab treatment than those who had the A/A or A/G genotype [38]. They studied the influence of the TNF –308 A/G polymorphism on long-term responses to infliximab in a prospective fashion in 22 consecutive patients. Patients who had the A/A or A/G genotype were compared with those who had the G/G genotype. After 24 months of treatment with infliximab, patients with the –308 G/G genotype had a better response to infliximab treatment than those who had the A/A or A/G genotype [38].
significantly better response (mean decrease in DAS28 –2.4; p<0.01) than patients in the other groups. The study also demonstrated that the TNF –308 A/G genotype was associated with sustained (>1 year) high disease activity and functional decline despite treatment with infliximab, suggesting that carrying the A allele may portend a more severe disease course in RA with a poorer response to treatment.

Guis et al. reported that RA patients with the –308 G/G genotype responded better to etanercept than patients with the –308 A/G or A/A genotypes [39]. The study involved 86 RA patients who were treated with etanercept and genotyped for the –308 A/G TNF polymorphism. Patients were subdivided into group A (A/A and A/G genotypes) and group G (G/G genotype). The clinical response to etanercept in groups A and G was compared after 6 and 12 months, using the DAS28. After a 6-month treatment period, 55.6% of patients in group A and 82.4% of patients in group G had a DAS28 improvement of >1.2 (p=0.027). After 1 year of treatment, among 48 patients followed up, 47% of patients in group A and 87% in group G maintained an improvement in DAS28 >1.2 (p=0.005).

Kang et al. studied several genetic polymorphisms within the TNF and LT-α gene region and showed that the –857 C/T SNP in the promoter region of the TNF gene was associated with response to etanercept [40]. In this study, 70 Korean patients were examined to determine whether these polymorphisms were associated with treatment outcome with etanercept. Patients were divided into responders and non-responders according to the ACR20 and ACR70 response criteria. Only the –857 C/T SNP was significantly associated with response; the frequency of the T allele was 5% in the ACR20 non-responders and 39% in the ACR70 responders (odds ratio [OR] 12, 95% confidence interval [CI] 1.4–105; p=0.0077). Among ACR70 responders, there were more carriers of the T allele (39%) than the C allele (13%), although this did not reach statistical significance. Moreover, the ratio of ACR70 responders to ACR20 non-responders among the T-allele carriers was >10-fold higher than in the C allele homozygotes (OR 12, 95% CI 1.2–120; p=0.033), indicating that this SNP may be a useful genetic marker for predicting response to etanercept.

A recent pharmacogenetic study by Miceli-Richard et al. suggested that a particular TNF haplotype

Figure 1. Chromosomal location of the TNF-α gene and polymorphisms in the region.
Table 1. Summary of pharmacogenetic studies of TNF antagonists in RA.

<table>
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<tr>
<th>Gene/polyorphism</th>
<th>Postulated function of polymorphism</th>
<th>Possible clinical effect</th>
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<td>Transcription/production of TNF-α</td>
<td>TNF –857 T-allele was associated with positive response to etanercept in RA</td>
<td>[40]</td>
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<tr>
<td>TNF –308</td>
<td>Transcription/production of TNF-α</td>
<td>TNF –308 GG was associated with positive response to infliximab and etanercept in RA</td>
<td>[38,39]</td>
</tr>
<tr>
<td>TNF –238</td>
<td>Transcription/production of TNF-α</td>
<td>TNF –238 G-allele was associated with negative response to adalimumab in RA</td>
<td>[41]</td>
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<tr>
<td>IL10 microsatellites</td>
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<td>[42]</td>
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<tr>
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<td>Binding to IgG leading to phagocytosis</td>
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<tr>
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<td>Influence on severity and susceptibility to RA</td>
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<td>[43]</td>
</tr>
</tbody>
</table>

IgG: immunoglobulin G; IL-10: interleukin-10; FcγRIIIA: Fcγ receptor type IIIA; HLA: human leukocyte antigen; RA: rheumatoid arthritis; SE: shared epitope; TNF-α: tumor necrosis factor-α.

(–238G/–308G/–857C) may be associated with a lower rate of response to adalimumab in RA patients [41]. The investigators studied 388 patients receiving adalimumab alone or in combination with a disease-modifying antirheumatic drug (DMARD). All patients were genotyped for the HLA-DRB1 shared epitope (SE) alleles and three TNF gene polymorphisms (–238A/G, –308A/G, and –857C/T). Extended haplotypes spanning the HLA-DRB1 and TNF loci were constructed. Neither the number of HLA-DRB1 SE copies nor the presence of the three individual TNF polymorphisms was significantly associated with an ACR50 response to adalimumab at 12 weeks. However, the –238G/–308G/–857C haplotype was associated with a lower rate of ACR50 response to adalimumab at this time point (34% vs. 50% in patients without the haplotype; p=0.003).

**IL-10 microsatellite polymorphisms**

A recent study by Schotte et al. looked at microsatellite polymorphisms in the IL10 gene as predictors of response to etanercept therapy [42]. The IL10 microsatellites IL10.R and IL10.G were genotyped in 50 RA patients. Patients were treated for up to 4 years with etanercept and the treatment response was assessed by the EULAR criteria. IL10.R3 and the ILR3-G9 haplotype were associated with a good response to etanercept (OR 5.5, 95% CI 1.6–18, and OR 5.1, 95% CI 1.5–18, respectively). In addition, IL10.G13 and the IL10.R2-G13 haplotype were more common among patients with a moderate or no response to etanercept (OR 0.18, 95% CI 0.05–0.61, and OR 0.14, 95% CI 0.04–0.50, respectively). These results suggest that microsatellite polymorphisms in the IL10 gene may play a role in determining response to etanercept in RA patients.

**Fcγ receptor polymorphisms**

Tutuncu et al. investigated the Fcγ receptor type IIIA (FcγRIIIA) polymorphism and demonstrated that the FcγRIIIA-158 F allele was a marker of favorable response to anti-TNF therapy [37]. The study was designed to assess the clinical outcome in 35 patients with RA and psoriatic arthritis treated with the three anti-TNF agents (adalimumab, etanercept, and infliximab). Each patient's rheumatologist was asked to categorize the patient as a good responder or a poor responder based on physician's global assessment of disease activity. All patients were genotyped for the FcγRIIIA-158 polymorphism. The distribution of the FcγRIIIA-158 genotype was as follows: F homozygous (F/F) 31.5%, V homozygous (V/V) 11.5%, and VF heterozygous (V/F) 57%. Among very good responders (n=23), the distribution of alleles was as follows: F/F 48%, V/V 13%, and V/F 39%. Among non-responders (n=12), the distribution of alleles was as follows: F/F 0%, V/V 8%, and V/F 92% (p<0.01). Thus, the FcγRIIIA-158 F allele appeared to be a marker of response to anti-TNF therapy.

**IL-1RN/SE polymorphisms**

Marotte et al. investigated IL1RN and TNF polymorphisms in 198 RA patients and found that these polymorphisms did
not predict the clinical response to infliximab [43]. The study sought to determine whether the response to infliximab was associated with SE carrier status or selected cytokine gene polymorphisms in IL1RN and TNF (including the −308G/A promoter polymorphism). The response to infliximab was defined using ACR response rates. Neither SE carrier status nor the polymorphisms predicted response to infliximab. However, the authors demonstrated an association between selection for infliximab treatment and SE status, in that patients with the SE were almost twice as likely to be selected for infliximab treatment (OR 1.89, 95% CI 1.35–2.65; p<0.001). In addition, a dose effect was observed between the SE copy number and selection for infliximab treatment; patients with one SE copy were 1.5 times more likely (OR 1.58, 95% CI 1.09–2.27; p=0.01) and patients with two copies three times more likely (OR 2.96, 95% CI 1.92–4.56; p<0.001) to be selected for infliximab treatment than those with no copies of the SE allele.

Discussion
Although biological therapies blocking TNF-α constitute a major advance in the management of RA, selection of RA patients for these therapies is still empirical and there are no standard guidelines. Pharmacogenetic testing has significant potential to optimize therapy with these agents in RA patients, but there are certain facts about the studies reviewed in this article that need to be considered (Table 1). Most of these studies had small sample sizes and hence were underpowered, raising questions about the validity and generalizability of the results. In addition, considerable contradiction exists amongst the available studies. For example, some studies showed a positive association between the TNF −308 G/G genotype and response to infliximab and etanercept [38,39], while others demonstrated no such association [40,43]. More importantly, given the central role of TNF in the pathophysiology of RA, polymorphisms in the TNF locus may potentially influence disease severity and this fact should be taken into account when interpreting such pharmacogenetic data. For instance, Fonseca et al. observed that the TNF-α −308 A/G genotype was associated with high disease activity and functional decline, despite treatment with infliximab [38]. Hence, it may be difficult to differentiate between the effects of the TNF polymorphisms on RA disease activity and severity, and response to anti-TNF therapy.

Summary
In summary, although the results of recent pharmacogenetic studies on the TNF antagonists in RA are intriguing, they remain hypothesis-generating and need to be replicated and validated in larger patient populations. The greatest challenge to the incorporation of pharmacogenetic testing into clinical care is not the availability of technologies to determine large numbers of genotypes, but rather the precise definition of drug-response phenotypes. Large, well-powered clinical trials are needed before genotype-guided therapy can be incorporated into routine clinical care [15]. Furthermore, rather than single SNP association studies, large multicenter studies examining composite SNPs and haplotypes may be more useful in defining the genotypes that determine drug response. With rapid advances in the International HapMap Project (www.hapmap.org) and the dedication of major funding agencies to pharmacogenetics research (www.nigms.nih.gov/pharmacogenetics), such studies should be feasible and available in the near future.

Disclosures
The authors have no relevant financial interests to disclose.
The mortality rate in rheumatoid arthritis (RA) is higher than that in the general population, and standardized mortality ratios (SMRs) range from 1.3–3.0 [1]. This increased mortality rate is largely attributable to cardiovascular disease (CVD), principally atherosclerosis. CV morbidity also appears to be at least two-fold greater in RA in comparison with the general population [2]. The raised CV risk in RA may have several causes. Firstly, the prevalence of CV risk factors, such as dyslipidemia, diabetes mellitus, hypertension, a higher body mass index (BMI), a higher waist-to-hip ratio, or lack of physical activity, may be increased. Secondly, in chronic diseases, unrelated disorders such as hypertension are frequently under-treated [3,4]. Finally, the chronic inflammatory process in RA might itself mediate a higher CV risk.

**Cardiovascular mortality**

Most studies indicate that the risk of dying from CV disease in RA, particularly coronary heart disease, is increased by more than two-fold in comparison with the general population. However, some recent reports described no enhanced mortality rate in RA, which might be due to the inclusion of inception cohorts (as the enhanced mortality rate becomes more apparent after 10 years of disease duration) [1,5]. Another possible explanation for this discrepancy might be the more intensive treatment of RA employed nowadays, which leads to a longer overall life expectancy. Nevertheless, this survival improvement remains below that of the general population; thus, SMRs remain enhanced. This is illustrated by a recent study in which no reduction in mortality rate was observed; in fact, a relative increase in comparison with the general population was seen [6]. The mortality rates between 1965 and 2005 were relatively constant at 2.4 and 2.5 per 100 person-years for female and male RA patients, respectively. In contrast, the expected mortality rate in female population control subjects declined from 1.0 in 1965 to 0.2 per 100 person-years in 2000. For male subjects, these figures were 1.3 and 0.2 per 100 person-years in 1965 and 2000, respectively. These findings indicate a widening mortality gap between RA patients and the general population.

**Cardiovascular morbidity**

As stated above, several investigations have indicated an elevated rate of CVD in RA. In a prospective Dutch study, the magnitude of this enhanced CV risk relative to that conferred by type 2 diabetes – a well-established CV risk factor – was investigated [2]. The prevalence of CVD was determined in 353 RA patients in the CARRÉ (Cardiovascular Research and Rheumatoid Arthritis) study, and in participants of a population-based cohort study on CVD and...
its risk factors (the Hoorn study). Non-diabetic RA patients (n=294) were compared with non-diabetic, non-RA individuals (n=258), and individuals with type 2 diabetes (n=194) from the Hoorn study. The adjusted odds ratios (OR) for CVD were 3.1 in RA patients and 2.3 in individuals with type 2 diabetes in comparison with non-diabetic individuals. This investigation indicates that the prevalence of CVD in RA is at least comparable with its prevalence in diabetes, and is increased at least two-fold relative to the general population.

**Myocardial infarction**
RA patients who experience a myocardial infarction (MI) have an approximately doubled rate of multivessel coronary disease in comparison with MI patients without RA, indicating accelerated atherosclerosis in RA [7]. In addition, the case fatality rate in RA patients following an MI is almost two-fold greater than that in individuals without RA [8,9]. It is also important to realize that RA patients are less likely to report angina and are twice as likely to have a silent MI and sudden death in comparison with the general population [10].

To date, two follow-up studies with CV endpoint assessment have been published. In the first, 234 patients with RA were followed up for 1 year, and 15 CV events (predominantly MIs) occurred during 252 patient-years [11]. As a comparator group, >4600 participants of a community-based cohort were followed for up to 8 years; in this group, 200 CV events occurred. The age- and sex-adjusted incidence risk ratio of CV events associated with RA was 4.0 (95% confidence interval [CI] 1.86–8.43), which decreased to 3.2 when adjusting for CV risk factors. The second study considered the 3-year follow-up of the CARRÉ investigation [12]. In that analysis, CV events were reported in 9% of the RA patients and in 4% of the general population. The age- and gender-adjusted relative risk (RR) of a CV event was 2.0 (95% CI 1.3–3.1).

**Congestive heart failure**
One of the first investigations revealing an increased likelihood of congestive heart failure in RA indicated an RR of 1.6 during follow-up of 450 RA patients and 450 control subjects [13]. A much larger sample of patients came from the National Data Bank for Rheumatic Diseases [14]. A total of 13 171 RA patients and 2568 osteoarthritis patients were followed over a 2-year period; heart failure was observed in 461 (3.9%) of those with RA and in 87 (2.3%) osteoarthritis patients. Other database investigations have indicated similar results. However, an important pitfall of the heart failure studies is that diagnosis has always been based on clinical criteria, rendering it less reliable. Obviously, the use of echocardiography for assessment of heart failure might solve this problem. In this regard, congestive heart failure is generally the result of either systolic or diastolic ventricular dysfunction, and an increased frequency of left ventricular diastolic dysfunction has been found in patients with long-standing RA who do not have CV risk factors or clinically evident CV manifestations [15]. Moreover, an increased frequency of subclinical pulmonary hypertension has also been identified in these patients compared with matched controls.

**Stroke**
Wolfe et al. reported the results of a US survey of CV in 9093 RA patients and 2479 osteoarthritis patients [16]. Compared with osteoarthritis patients, RA patients had an OR of 1.7 (95% CI 1.3–2.2) for current stroke and an OR of 1.1 (95% CI 0.9–1.2) for lifetime stroke. In contrast, Solomon et al. followed 25 385 British Columbian adults with RA over 5 years and found an incidence rate per 1000 years of 5.1 in RA and 2.7 in non-RA subjects, resulting in a rate ratio of 1.9 (95% CI 1.7–2.1) [17]. Another database investigation in 11 633 RA patients in the UK, with a follow-up of 5 years, revealed an incidence rate of stroke of 7.0 per 1000 patient-years and a relative risk of 1.4 (95% CI 1.3–1.5) versus non-RA subjects [18]. These data strongly suggest that the risk for stroke is enhanced in RA patients, although the increase may be less in comparison with the risk for an MI.

**Peripheral arterial disease**
A database investigation from an integrated US health plan including 28 208 RA patients revealed a prevalence of peripheral arterial disease of 4.7 in RA patients and 1.7 in matched controls (OR 2.3; 95% CI 2.3–2.6) [19]. Liang et al. found a 30-year cumulative incidence rate of peripheral arterial disease of 20% in 609 incident RA patients who were diagnosed during 1955–1994 and followed up to the year 2000 [20]. This is approximately 30% higher than would have been expected from prevalence data in non-RA subjects [20]. In an elegant study, Del Rincón et al. investigated the stiffness of limb arteries as a marker for peripheral arterial disease in 234 RA patients and 102 control subjects [21]. Among the RA patients, 66 of 931 arteries (7%) were incompressible and 30 (3%) were obstructed; for the control subjects, the percentages were 0.7% and 1%, respectively.

**Preclinical atherosclerosis**
It is increasingly acknowledged that carotid artery intima-media thickness (IMT) is an important marker for early, preclinical atherosclerosis and a strong predictor of future CV events. IMT is assessed non-invasively with
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echocardiographic techniques (carotid ultrasound). In a landmark study of 4476 general population persons followed for 6 years, every 0.20 mm increase of the maximum IMT of the common carotid artery was associated with a 30% increase in the incidence of new CV events [22]. Consequently, carotid artery IMT in RA has been assessed by several investigators. One of the first studies was conducted by Japanese researchers who found significantly increased common carotid IMT in 138 RA patients (mean age 55 years) in comparison with 94 matched controls (mean age 52 years), with values of 0.64 mm and 0.58 mm, respectively (p<0.05) [23].

Accurate longitudinal data on the progression of subclinical atherosclerosis in RA are still sparse, but data were recently indirectly derived from a cross-sectional investigation. del Rincón et al. found that the rate at which the IMT increased was related to disease duration and ranged from 0.15 mm/10 years among RA patients with a disease duration of <7 years, to 0.30 mm/10 years in RA patients with a disease duration of >20 years [24]. Therefore, patients with prolonged RA have more advanced atherosclerosis than patients of the same age but who have a shorter disease duration, which suggests that RA accelerates atherosclerosis. This is in line with the observation that atherosclerosis represents a chronic inflammatory process of the artery and, therefore, that longer RA disease duration will lead to a greater atherosclerotic burden (discussed below in “Atherosclerosis and inflammation”). Gonzalez-Juanatey and colleagues recently found that carotid artery IMT had a high predictive power for the development of CV events over a 5-year follow-up period in 47 patients with RA who did not have clinically evident CV disease at the time of the carotid ultrasonography evaluation [25].

An emerging technique for assessing coronary atherosclerosis, including preclinical disease, is the determination of coronary artery calcification by computed tomography [26]; the presence of such coronary calcifications is a strong predictor of subsequent coronary heart disease. Chung et al. found coronary calcification in 61% of patients with established RA, 43% of early RA patients, and in 38% of control subjects [27]. The OR for more severe coronary calcification was 3.4 in patients with established disease. The relationship between coronary calcification and RA disease duration was recently confirmed in another study [28].

Cardiovascular risk factors in RA

Dyslipidemia

Increased levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), and a decreased level of high-density lipoprotein cholesterol (HDL-C) are associated with a higher CV risk. The available literature on lipid profiles in patients with RA is contradictory but it appears that there is an inverse relationship between disease activity and lipid levels [29].

When does the dyslipidemia start?

Dyslipidemia is already present in early RA and so the question of whether or not this phenomenon starts in the preclinical phase of the disease has emerged. Hence, the present author and colleagues have investigated the lipid profile over time, and its relationship with inflammation, in subjects who later developed RA [30]. Future RA patients displayed 4% higher TC, 9% lower HDL-C, and 17% higher triglyceride levels than matched controls (p<0.05), at least 10 years before the onset of symptoms. Although the differences between the various lipid values were small, they are clinically relevant, particularly in the light of results from other studies [31].

Functional properties of lipid particles

Protecting LDL from oxidation is one the anti-atherogenic roles of normal HDL. This anti-inflammatory HDL is distinct from the so-called pro-inflammatory HDL, which is devoid of these properties and may actually promote atherosclerosis. Indeed, in a small study that included 48 women with RA and 72 healthy subjects, McMahon and colleagues showed that pro-inflammatory HDL was detected more frequently in RA patients (20%) than in control subjects (4%) [32].

Antirheumatic treatment and lipid profile

Treatment with disease-modifying antirheumatic drugs (DMARDs) has beneficial effects on the lipid profile in patients with early active RA [33]. These agents do mediate an increase in TC, but they induce a more pronounced increase in HDL-C, resulting in a lower (more favorable) atherogenic index (TC/HDL-C ratio), which is an important prognostic CV risk factor.

Investigations of tumor necrosis factor (TNF)-blocking agents reveal a transient increase in TC and HDL-C levels, mostly accompanied by improvement of the atherogenic index, during the first few months of the treatment. Thereafter, the results become divergent between the studies (reviewed in [33]). This may be due to differences in disease activity, changes in co-medication (particularly prednisone), dietary intake, and physical activity. Hence, future studies should appropriately address these potential confounders in order to reach valid conclusions.

Lifestyle factors and medical comorbidities

Smoking is an important risk factor for CV disease in the general population. It is conceivable that smoking might play a role in CV disease in RA as it increases the susceptibility for the development of RA as well its severity.
A recent investigation revealed that smoking was more prevalent in RA patients and that there was an increased CV risk in these subjects compared with that in non-smoking RA patients [35]. However, the effect of smoking was significantly less than that observed in control (non-RA) subjects (hazard ratio [HR] for CV disease was 1.3 and 2.2 for smoking vs. non-smoking RA patients and smoking vs. non-smoking controls, respectively).

Published data on the prevalence of type 2 diabetes in RA are not concordant; however, as there is increasing evidence for elevated rates of insulin resistance in RA [36], it is conceivable that the prevalence of diabetes might be enhanced. Similarly, data regarding hypertension in RA are contradictory and no conclusions can be reached with respect the contribution of body mass index to the CV risk in RA.

In summary, the abovementioned evidence is not uniform, adequate comparative investigations are lacking, and studies are limited by a lack of control for important confounders. Nevertheless, the prevalences of hypertension and smoking appear to be increased in RA patients.

Very recently, a systematic review investigated the effectiveness of exercise interventions in patients with RA [37]. Unfortunately, no studies investigating the effect of exercise interventions in relation to CV disease in RA were identified. Therefore, further studies are required to address this topic.

**Under-treatment of hypertension in RA**
It is well known that comorbidity is under-treated in patients with chronic diseases [38]. Moreover, it is known that comorbidities in patients with RA do not differ from comorbidities observed in other chronic diseases [39]. Thus far, just one study has addressed this topic [4], with a total of 400 consecutive RA patients investigated for hypertension and antihypertensive drug use. Hypertension was present in 71% of the patients; only 61% of these received antihypertensives. These results clearly indicate that future research in this area is necessary.

**Atherosclerosis and inflammation**
Formerly, atherosclerosis was seen as an accumulation of lipids within the arterial wall. However, during the last few decades, it has become acknowledged that atherosclerosis represents a chronic inflammatory process in the artery (Fig.1). Endothelial dysfunction is the first step of atherosclerosis and is induced by different cardiovascular risk factors, e.g. oxidized LDL-C, smoking, hypertension, or diabetes. The endothelium becomes more permeable to lipoproteins and acquires procoagulant rather than anticoagulant properties. Increased permeability to inflammatory and muscle cells also occurs. Inflammatory mediators such as TNF-α and interleukin-1 cause increased binding of (modified) LDL-C to the endothelium and muscle cells. Modified LDL-C accumulates within macrophages resulting in the formation of foam cells and subsequent fatty streaks. This lesion progresses and a fibrous cap is formed, which consists of smooth muscle cells and a collagen matrix that separates the atherosclerotic plaque lesion from the arterial lumen [40,41].

During this process, the arterial wall becomes thicker; however, initially, the lumen remains unaltered owing to dilatation. Accumulation and activation of macrophages and T lymphocytes leads to the release of several mediators causing further damage, and, ultimately, narrowing of the artery does occur. Platelet activation by the dysfunctional endothelium results in the formation of thromboxane – a potent vasoconstrictor and platelet aggregator. Finally, plaque rupture and thrombosis leads to unstable angina or MI. This process accounts for up to 70% of the acute coronary syndromes [41]. The cellular interactions that are seen in the development of atherosclerosis are similar to those observed in chronic inflammatory diseases such as RA, which might explain the increased CV risk in patients with RA. In keeping with this view, high-resolution B-mode ultrasound of the common carotid artery identified a strong correlation between the carotid IMT and markers of systemic inflammation in patients with RA and in healthy subjects [24,42].

**Antirheumatic treatment and CV risk in RA**

**Acetaminophen**
Chan et al. examined the relationship between acetaminophen use and major CV events in a prospective cohort of 70 971 women [43]. Frequent usage, defined as on ≥22 days/month, was linked with an elevated risk of CV events. The highest risk was associated with the intake of ≥15 tablets per week (RR 1.7, 95% CI 1.1–2.6), with 69% of patients taking tablets of ≥500 mg acetaminophen. The observed association might be mediated through the induction of hypertension due to cyclooxygenase-2 (COX-2) inhibition [44].

**Glucocorticoids**
The place of glucocorticoids in RA therapy is a continuing matter of debate in view of their associated CV side effects, which include hypertension, dyslipidemia, insulin resistance, and diabetes. These side effects are particularly linked to prolonged exposure to high-dose glucocorticoids, with hypertension demonstrated to be especially prominent in patients receiving ≥7.5 mg/day prednisone for a period of ≥6 months [45]. Conversely, low-dose glucocorticoids might have beneficial effects on the lipid profile [46].

There is no doubt that corticosteroids rapidly and effectively suppress inflammation in RA and their use may be justified as a short-term treatment, e.g. as a “bridging
**Figure 1.** Effects of T cell activation on plaque inflammation. Antigens presented by macrophages and dendritic cells (antigen-presenting cells) trigger the activation of antigen-specific T cells in the artery. Most of the activated T cells produce Th1 cytokines (e.g. IFN-γ), which activate macrophages and vascular cells, leading to inflammation. Regulatory T cells modulate the process by secreting anti-inflammatory cytokines (such as IL-10 and TGF-β).

IFN-γ: interferon-γ; IL-10: interleukin-10; LDL: low-density lipoprotein; TGF-β: transforming growth factor-β; Th1: type 1 helper T cell. Redrawn with permission from [41].
therapy” during the period between the initiation of and response to DMARDs [47]. The debate regarding the use of corticosteroids continues.

**Nonsteroidal anti-inflammatory drugs and COX-2-selective inhibitors**

During the last decade there has been an ongoing debate as to whether or not COX-2-selective inhibitors (COXIBs) are associated with an enhanced CV risk, particularly MIs. Several large-scale, placebo-controlled trials have demonstrated that COXIBs are accompanied by an approximately two-fold enhanced CV risk [48,49].

There are many observational database studies indicating either an increased or no increased CV risk with nonsteroidal anti-inflammatory drug (NSAID) therapy. Observational investigations have inherent methodological problems that can only be addressed by the performance of large-scale, randomized investigations. However, such studies have not been conducted with NSAIDs. As an alternative (albeit a second-best option), meta-analyses with meta-regression techniques of comparative trials of NSAIDs and COXIBs can be employed in order to reach valid conclusions regarding the CV risks associated with NSAID use. From one such study, and a large controlled investigation comparing a COXIB with a non-naproxen NSAID, it appears that non-naproxen NSAIDs confer a similar CV risk to COXIBs [50,51].

**DMARDs**

In a prospective investigation of 1240 patients in which 190 patients died during a follow-up of 18 years, the CV mortality rate was 70% lower in patients receiving methotrexate than in those who did not receive the drug [52]. Another study revealed that patients who do not respond to methotrexate treatment have a poor prognosis [53]. Not only is CV mortality reduced by methotrexate; from two case–control studies, it appears that the use of methotrexate is also associated with less CV morbidity [54,55].

**TNF-blocking agents**

Jacobsson et al. linked a Swedish database – in which 921 of 1430 patients received TNF-blockers – with a national mortality register. The adjusted HR for death was 0.65 when comparing TNF blockade versus no TNF blockade [56]. In an earlier study, these investigators determined the incidence of MIs in 983 RA patients, of whom 531 underwent treatment with TNF blockers [57]. There were 13 CV events in the anti-TNF-treated patients resulting in 14 CV events per 1000 person-years, compared with 35 CV events per 1000 person-years in RA patients not treated with anti-TNF. The adjusted rate ratio was 0.46 in anti-TNF-treated compared with non-anti-TNF treated subjects. From a larger British cohort study, the risk of an MI was markedly reduced when comparing anti-TNF responders with the non-responders (incidence ratio 0.36) [58].

**Cardiovascular risk management in RA**

In summary, RA should be seen as a new CV risk factor, for which CV-risk management (CV-RM) is mandatory. CV-RM is generally performed on the basis of the 10-year absolute risk for a (fatal) CV-event, which is derived from a CV risk formula based on several CV risk factors. Examples include the Framingham risk calculator and the Systematic Coronary Risk Evaluation (SCORE). Treatment with statins and/or antihypertensives is then initiated at above a certain threshold, e.g. a 10-year CV-mortality risk of ≥10%. Thus far, CV risk function scores are not available for patients with RA and, therefore, existing CV risk functions such as SCORE should be adapted, for example by a multiplier, so that they can be used to assess the CV risk in RA patients. Regular CV risk screening appears to be appropriate for RA patients and lifestyle recommendations should be given to every patient. Treatment with statins and/or antihypertensives should be considered when the 10-year CV risk is above a certain value. In addition, aggressive suppression of the inflammation is recommended to further lower the CV risk [59].

**Disclosures**

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Serum Autoantibodies in Rheumatoid Arthritis

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Various antibodies have been found in the sera of patients with rheumatoid arthritis (RA). At present, rheumatoid factor (RF) is the only autoantibody included in the American College of Rheumatology criteria for the classification of RA, but its specificity is limited. New autoantibodies with different degrees of sensitivity and specificity have been described in recent years and a new class of autoantibodies directed against citrullinated peptides has also recently gained acceptance due to their high specificity, and diagnostic and prognostic value. These, together with other autoantibodies found in RA, are discussed in this review. Int J Adv Rheumatol 2008;6(2):47–52.

Rheumatoid arthritis (RA) is a common inflammatory disease of autoimmune pathogenesis. Since the 1940s, an antibody directed against the Fc portion of immunoglobulin G (IgG), known as rheumatoid factor (RF), has been measured by various methods in the sera of RA patients, and has a sensitivity of approximately 65–80%, but a limited specificity. RF may be positive in various autoimmune disorders and chronic infections, and also in some healthy subjects, particularly in the elderly. However, RF is currently the only autoantibody included in the American College of Rheumatology 1987 classification criteria for the diagnosis of RA [1]. Positivity for RF has been associated with more severe articular and extra-articular disease [2].

Serological markers other than RF have been investigated in RA, but most have shown a poor diagnostic sensitivity and specificity (Table 1). However, in the last decade, a new class of autoantibodies directed against citrullinated proteins has emerged as the most specific markers of RA identified to date, and have been shown to have important diagnostic and prognostic properties [3]. The present review discusses the autoantibodies other than RF described thus far in the sera of patients with RA and their clinical relevance, with particular emphasis on autoantibodies against citrullinated proteins.

**Anti-citrullinated protein/peptide antibodies**

Anti-citrullinated protein/peptide antibodies (ACPA) are a group of autoantibodies directed against peptides containing citrulline, an amino acid generated by a post-translational modification process, which involves deamination of the natural amino acid arginine by the enzyme peptidylarginine deiminase [4]. This group of autoantibodies is related to the antibodies recognized previously as antiperinuclear factor, antikeratin, or antifilaggrin antibodies. ACPA are regularly detected by an enzyme-linked immunosorbent assay (ELISA) using synthetic peptides containing citrulline. The first ELISA test using synthetic cyclic peptides derived from filaggrin (the CCP1 test) was improved to increase its sensitivity (CCP2 test) [5]. Other synthetic and non-synthetic antigenic substrates have been used to detect these antibodies, including citrullinated vimentin [6] and fibrin [7], and a more recent anti-CCP assay (CCP3) has been developed [8]. These tests have similar diagnostic (and probably prognostic) properties, but not the same reactivity, allowing the possibility of discrepancies, which are observed more commonly in non-RA samples and are due mostly to differences in the substrates used rather than other technical reasons [9–11].

**Diagnostic value**

In the last 5 years, many reports have confirmed the important diagnostic value of ACPA. The second generation anti-CCP assay (CCP2) – the best known and the most widely used test – has a sensitivity similar to that of RF (60–80%), but has a higher specificity (>95%) [12]. Approximately 30–40% of RF-negative RA patients test positive in the CCP2 assay. In a recent meta-analysis including 37 studies of anti-CCP antibodies and 50 studies on RF, it was concluded that anti-CCP is more specific than
Several reports have studied the predictive value of ACPA for arthritis [18]. In a 2-year follow-up of 524 patients with early arthritis, Visser et al. found that anti-CCP was the highest-weighted factor of the seven variables that predicted persistent arthritis after 2 years of follow-up in a series of 524 patients with early arthritis [18].

**Pathogenic significance**

The pathophysiological role of ACPA is unknown, although it is proven that the antibodies may be present years before the first clinical signs of RA [23]. In recent years, an association between ACPA and the rheumatoid (shared) epitope and the HLA-DRB04 genotype has been demonstrated [24]. Smoking has also been identified as a predisposing factor for RA, but only in anti-CCP-positive patients, and has a strong correlation with the DRB04 genotype [25,26].

Citrullinated proteins have been found in the synovium of patients with RA and other inflammatory joint diseases, probably as a consequence of apoptosis due to inflammation [12,27]. However, the immunological response to the generation of ACPA seems to be very specific for RA, in particular for carriers of the shared epitope [10]. A direct role for ACPA in joint damage has recently been suggested [28,29].

**Anti-RA-33 antibodies**

Anti-RA-33 antibodies, which are directed against the heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2) that is involved in mRNA transport and the regulation of alternative splicing, have recently been identified as a potentially specific serological marker for RA [30]. They have been found in nearly 35% of patients with established RA but not in control subjects [31]. In early RA, their sensitivity is approximately 30% [32], and in undifferentiated polyarthritis later classified as RA, anti-RA33 antibodies have shown a higher specificity than RF [32], suggesting that they are early antibodies in RA, and are more specific than RF.

Although anti-RA33 antibodies were initially thought to be a useful early, specific marker for RA, they are not strictly specific for RA as they are also found in nearly 20% of patients with SLE and 40–60% of patients with mixed
connective tissue disease (MCTD) [33], mainly in those with erosive disease [34]. However, in SLE and MCTD, they usually occur together with antibodies to U1-small nuclear ribonucleoprotein particle (U1-snRNP) or Sm. Anti-RA33 without concomitant anti-U1-snRNP antibodies have a specificity for RA of 96% [33]. One study has found that anti-RA-33 antibodies do not have a significant impact on radiographic outcomes [35].

**Anti-collagen type II antibodies**

The possibility that an immune response directed against joint-related antigens such as type II collagen could play a role in the pathogenesis of RA has been hypothesized in recent years. It has been suggested that an immune response to a foreign antigen that shares some epitopes present in type II collagen could produce antibodies not only to the antigen but also to the shared epitopes, producing joint inflammation by the binding of antibodies to the epitope on the collagen cartilage. The specific expression of type II collagen in articular cartilage and its ability to induce destructive arthritis in animal models reinforces this hypothesis [36].

Anti-collagen type II (anti-CII) antibodies have been demonstrated in serum and synovial fluid of approximately 30% of patients with RA [37], although lower frequencies have also been detected in patients with other rheumatic diseases, including SLE and systemic sclerosis (SSc), among others. In RA patients, a direct correlation between serum and synovial fluid titers of anti-CII and acute phase reactants has been found [38]. Anti-CII have been found mainly in early RA [39], and seem to have the potential to destroy cartilage in the early stages of RA. Besides the possible implication of anti-CII in the pathogenesis of RA, they could be a useful marker of cartilage destruction in some patients and could offer early information, before the disease becomes clinically evident.

Although some reports have suggested that anti-CII could be predictive of a more severe outcome [40], no differences with controls have been found in patients before the onset of RA [41]. This may be because anti-CII might only be produced after the onset of articular inflammation caused by other mechanisms. Thus, after breakdown of cartilage, exposure of collagen to the immune system could generate secondary antibodies against cartilage, and anti-CII could contribute to the perpetuation of inflammation.

**Anti-GPI antibodies**

Anti-GPI antibodies are directed against glucose-6-phosphate isomerase, a cytosolic enzyme that catalyzes the interconversion of D-glucose-6-phosphate and D-fructose 6-phosphate, which are essential bodily reactions. GPI also has cytokine and growth factor activities. Increased levels of anti-GPI antibodies have been found in the serum and synovial fluid of RA patients [42], with a prevalence ranging between 14.8% [43] and 64% [42].

Anti-GPI antibodies are not specific for RA relative to other rheumatic diseases [44,45], and no differences between early and established RA have been identified [43,46]. However, increased concentrations of anti-GPI have been found in RA patients with extra-articular manifestations such as nodules, vasculitis, or Felty’s syndrome [46]. No correlation between anti-GPI and other RA-associated antibodies, such as ACPA, has been found [43,45]. Furthermore, anti-GPI do not predict radiographic progression in very early arthritis. Therefore, anti-GPI antibodies provide only weak discrimination of RA from non-RA rheumatic disorders and are not a predictive factor for structural damage [45].

**Anti-BIP antibodies**

Autoanti-BIP antibodies against endoplasmic reticulum chaperone binding protein (anti-BIP), also called p68, have been found in the serum and synovial fluid of RA patients [47]. BIP stimulates synovial T cell proliferation, and its expression could be induced by a number of cellular stress mechanisms such as ischemia, heat shock proteins, or cytokines [48].

The sensitivity of anti-BIP for established RA is 63–73% and the specificity is 71–99% [47,48]. In early RA patients, the sensitivity of anti-BIP is 66% and the specificity is 65% [48]. The sensitivity of anti-BIP to predict the onset of RA – before disease onset – is 45%, and the specificity 65%. No correlation between anti-BIP and RF has been observed [47]. Anti-BIP antibodies have also been detected in patients with SS [49]. Recently, a reduction in serum anti-BIP levels was described in RA patients after biological therapy with TNF-α blockers [50]. However, no data on anti-BIP and disease progression or severity in early RA are available.

**Anti-calpastatin**

Calpastatin, the endogenous inhibitor of the intracellular, calcium-activated cysteine proteases calpain I and II is widely distributed in the cytoplasmic fraction of almost all mammalian cells [51]. Elevated levels of extracellular calpain have been reported in inflamed synovium, suggesting that calpain could be secreted by synovial cells and might play a role in cartilage degradation in RA [52]. Recently, various reports have associated anti-calpastatin antibodies with RA [53], venous thrombosis [54], and autoimmune infertility [55], although epitope mapping in calpastatin remains controversial. Mimori et al. detected anti-calpastatin antibodies in 57% of RA patients and in lower percentages of patients with SLE, polymyositis/dermatomyositis, or SSc,
and healthy controls [53]. Another study determined IgG anti-calpastatin antibodies in 58 RA patients and 24 subjects with osteoarthritis (OA), 18 with SLE, 19 with SSc, and five with SS, using a modified ELISA [56]. IgG anti-calpastatin antibodies were found in 48 (83%) out of 58 patients with RA and in only two patients with OA. IgG anti-calpastatin antibodies are both sensitive (83%) and specific (96%) for RA. In contrast, sera from patients with other systemic rheumatic diseases showed lower sensitivities (6% in SLE, 0% in SSc, and 20% in SS). Antibodies against C-terminal peptide and calpastatin domain I have been found in only a small proportion of RA patients and have not been associated with radiographic progression [57].

Recently, a strong association between anti-calpastatin antibodies, using an ELISA with purified synovial calpastatin as a substrate, and HLA-DRB alleles has been demonstrated [58]. The HLA-DRB1*0404 allele was very strongly associated with anti-calpastatin in RA sera. Eighty-three percent of patients expressing both HLA-DRB1*0404 and HLA-DRB1*0401 were positive for antibodies against synovial calpastatin.

**Anti-Ro (SSA) antibodies**

Anti-Ro (SSA) antibodies are associated with a variety of autoimmune diseases including SS, SLE, subacute cutaneous lupus, neonatal lupus, SSc, and RA. The reported frequency of anti-Ro in RA varies widely (3–15%), possibly due to differences in methods and study groups [59–61]. Anti-Ro antibodies have been associated with extra-articular manifestations such as xerophthalmia, xerostomia, scleritis, oral ulcers, purpuric vasculitis, amyloidosis, and specific autoantibody profiles including hypergammaglobulinemia, cryoglobulins, anti-double stranded DNA, and antimitochondrial antibodies. Boire et al. found that patients with anti-Ro antibodies had more severe disease and a greater requirement for immunosuppressive drugs [61], while their genetic profile showed a lower frequency of HLA-DR4 than anti-Ro-negative patients, although these results were not confirmed by another study [60]. Anti-Ro antibodies have also been identified as predictive markers of penicillamine and gold salt toxicity in RA [62].

**Antiphospholipid antibodies**

The frequency of anticardiolipin antibodies (aCL) in RA patients ranges from 12% to 48% [63–66]. aCL have shown a correlation with high levels of C-reactive protein and repeated miscarriages, RF and antinuclear antibodies (ANA), extra-articular manifestations, nodules, and hemolytic anemia in patients with RA [63–66].

aCL have been linked with a higher risk of atherosclerosis in patients with RA. Pahor et al. evaluated internal carotid artery intima-media thickness and antiphospholipid (aPL) in a selected group of 70 patients with RA (non-diabetic, non-hypertensive, premenopausal women) and compared them with age- and sex-matched controls [67]. There was a significantly higher internal carotid artery intima-media thickness and a greater number of plaques in RA patients compared with controls. IgG and IgM aCL were present in 15.7% of RA patients compared with 5% of the control group, whilst anti-β2GPI antibodies were positive in 30% of RA patients compared with 7.5% of controls. Seriolo et al. evaluated aPL and plasma levels of protein S in 184 patients with RA and extra-articular involvement [68]. Thirty-five (19%) had at least one type of aPL. Lupus anticoagulant was present in seven patients with concomitant aCL positivity. Thrombotic events were diagnosed in 34% of aCL-positive patients with RA. Low free protein S levels were found in 22 of 184 RA patients; 11 of those who had low free protein S levels and were positive for aCL. RA patients with positive aCL and a history of arterial and/or venous thromboses showed lower levels of free protein S compared with patients with positive aCL but no history of thrombosis. aCL has also been found in a small proportion of patients with RA who were treated with TNF-α antagonists. The clinical implications of these drug-induced aCL are unknown, but the majority of patients exhibit no clinical features related to antiphospholipid syndrome [69].

**Antineutrophil cytoplasmic antibodies**

Antineutrophil cytoplasmic antibodies (ANCA) are directed against lysosomal enzymes of human neutrophils and monocytes and have been identified in various vasculitides, especially in Wegener’s granulomatosis and microscopic polyangiitis. ANCA (perinuclear ANCA [pANCA] and cytoplasmic ANCA [cANCA]) have been detected in the sera of 0–70% of RA patients [70–72]. ANCA antibodies from RA patients recognize different antigens in the nucleus and cytoplasm, of which lactoferrin is the most common [73]. It has been suggested that ANCA occur especially in RA patients with longstanding, severe disease who are positive for RF and ANA. An association between ANCA and vasculitic and pulmonary involvement has also been proposed [70,71]. Mustila et al. evaluated the prevalence of ANCA in patients with early (<12 months) RA [70]. pANCA were found in 40 (50%) patients and atypical cANCA in three (4%) patients at study entry. pANCA were significantly more frequent in RF-positive patients. There was no correlation between ANCA and clinical disease activity. During follow-up, radiographic erosions (Larsen score) advanced more rapidly in pANCA-positive patients. Anti-myeloperoxidase (MPO), a pANCA-specific antibody, was determined in 97 patients with RA. Anti-MPO were detected
in 12 (12%) patients and were associated with nodules, lung involvement, and a higher swollen joint count [72].

Conclusion
Since the first description of RF >50 years ago, various autoantibodies have been found in the sera of RA patients. The majority of these have been shown to be more prevalent in RA than in other rheumatic diseases or healthy subjects although their sensitivity and specificity (Table 1) have consistently been shown to be lower than that of RF, and few appear to have prognostic significance. Variable results have been obtained for some of these autoantibodies, such as those directed against calpastatin, owing to technical difficulties and the characteristics of the antigenic substrate used.

However, in the last decade, ACPA have been identified as the most specific serological marker of RA, with interesting diagnostic and prognostic properties. These autoantibodies are now a useful tool for the diagnosis of RA in clinical practice and their role in the disease process and joint damage merits further investigation.

Disclosures
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Case Study Editor: Cornelia F Allaart, MD, PhD

Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands


**Case**

A 45-year-old woman of Moroccan descent was admitted to the present authors’ hospital with persistent convulsions. She had a history of systemic lupus erythematosus (SLE) based on the presence of arthritis, discoid skin lesions, positive antinuclear antibodies (ANA), antibodies to double-stranded DNA, and a positive Coombs test. In 1998, she suffered an intra-uterine fetal death due to antiphospholipid syndrome and in 2005, she was treated for biopsy-proven lupus nephritis (World Health Organization grade V). In 2006, she had a middle cerebral artery stroke with a grade four mitral valve insufficiency due to Libman–Sacks endocarditis; this resulted in left-sided spastic hemiparesis and a relapse of SLE glomerulonephritis for which she was treated with high-dose methylprednisolone and azathioprine. After the stroke the subject suffered epileptic fits for which valproic acid was started.

The current admission was due to sudden onset of generalized convulsions preceded by 1 day of progressive abdominal pain. There had been no fever or signs of infection, or neurological deficit. On admission, her medication consisted of phenprocoumon, prednisone 5 mg twice daily, azathioprine 50 mg three times daily, hydroxychloroquine 400 mg once daily, alendronic acid 70 mg per week, valproid acid 500 mg twice daily, amlodipine 10 mg once daily, peridinpril 8 mg once daily, atorvastatin 10 mg once daily, and pantoprazole 20 mg once daily.

**Examination**

On admission, the patient had already received clonazepam for generalized convulsions. She was unconscious with a Glasgow coma scale of 8. Her blood pressure was 180/100 mmHg, pulse rate 130 beats/min (bpm), and her temperature was 39.1°C. Auscultation of the heart revealed normal heart tones with a murmur consistent with the known mitral valve insufficiency. Examination of the lungs and abdomen revealed no abnormalities. Neurological examination revealed no signs of meningitis or asymmetric deficit; however, the head and eyes were fixed to the left.

The patient's laboratory tests on admission showed a normal hemoglobin level (8.3 mmol/L), white blood cell count (12.6x10\(^9\)/L), and platelet count (170x10\(^9\)/L), an erythrocyte sedimentation rate of 31 mm/h, C-reactive protein level of 3 mg/L, and an international normalized ratio (INR) of 4.0. Her sodium concentration was slightly decreased (133 mmol/L) and the elevated creatinine level (due to her chronic renal insufficiency) remained stable at 146 μmol/L. Liver enzymes were unremarkable. Spinal tap opening pressure was normal, and the spinal fluid leukocyte count was 2.0 cells per 3 μL with a total protein concentration of 1.19 g/L. Blood, urine, sputum, and spinal fluid cultures were all negative for abnormalities.

The electrocardiogram showed a sinus tachycardia of 120 bpm without abnormalities. Chest radiography and ultrasound of the abdomen also revealed no irregularities. A cardiac ultrasound did not indicate cardiac embolism or active Libman–Sacks endocarditis. Computed tomography (CT) scanning and magnetic resonance imaging (MRI; both standard and with Gadolinium contrast) of the brain revealed only old lesions consistent with the previous
ischemic stroke and old brain white matter lesions centrally on both sides. No tumor or hematoma was found on the brain scans. Thus far, no obvious causes for the persistent convulsions and the fever were identified.

Management and further progress
At this point, our differential diagnosis was convulsions due to her past stroke currently triggered by high fever of unknown infectious origin during immunosuppressives or by active SLE. Clonazepam and carbamazepine were administered intravenously and broad spectrum antibiotics were started. Over the next few days her fever subsided and she was awake and responsive. The laboratory results remained unchanged. One week later she developed a flaccid paresis of the right arm and leg together with phatic problems. New MRI of the brain and cervical spine (standard and with Gadolinium contrast) showed no signal abnormalities, no mass in the cervical cord, unchanged abnormalities in the brain, and no new ischemic lesions. This could neither prove nor rule out neuropsychiatric SLE (NPSLE). Due to the clinical deterioration in spite of the current treatment, active NPSLE was considered the most likely diagnosis. Therefore, methylprednisolone 1000 mg/day for 3 days was initiated, followed by 60 mg/day of prednisone. The anti-epileptic drugs were continued intravenously. Initially, a mild clinical improvement seemed to occur; however, during the next 2 days she had two more seizures. The paresis progressed to flaccid tetraparesis, soon followed by a critical respiratory failure for which an intensive care unit (ICU) admission was needed for mechanical ventilation. After exclusion of vascular or infectious causes, the neurological deterioration was thought to be due to active NPSLE in the form of Guillain–Barré syndrome (GBS). However, serial nerve conduction studies showed axonal rather than demyelinating findings, and needle electromyography showed no spontaneous activity. In other words, the typical GBS pattern was not observed. Nevertheless, treatment was started with intravenous immunoglobulin and cyclophosphamide pulse therapy (750 mg/m² [1]; prednisone 60 mg/day and the anti-epileptic drugs were continued. Initially, a mild clinical improvement seemed to occur; however, during the next 2 days she had two more seizures. The paresis progressed to flaccid tetraparesis, soon followed by a critical respiratory failure for which an intensive care unit (ICU) admission was needed for mechanical ventilation. After exclusion of vascular or infectious causes, the neurological deterioration was thought to be due to active NPSLE in the form of Guillain–Barré syndrome (GBS). However, serial nerve conduction studies showed axonal rather than demyelinating findings, and needle electromyography showed no spontaneous activity. In other words, the typical GBS pattern was not observed. Nevertheless, treatment was started with intravenous immunoglobulin and cyclophosphamide pulse therapy (750 mg/m² [1]; prednisone 60 mg/day and the anti-epileptic drugs were continued. Unfortunately, no improvement was observed.

In the ICU, the patient’s urine was noted to have an orange/reddish color, and at that moment acute porphyria (AP) was considered. Testing revealed elevated urine levels of total porphin of 24 306 nmol/24 h (normal <210 nmol/24 h), porphobilinogen of 269 μmol/24 h (normal <9 μmol/24 h), and δ-aminolevulinic acid (δ-ALA) of 300 μmol/24 h (normal <53 μmol/24 h). Fecal coproporphyrin levels were significantly elevated, with 86 nmol/g coproporphyrin I (normal <5.4 nmol/g) and 691 nmol/g coproporphyrin III (normal <2 nmol/g). This led to the diagnosis of an AP attack due to hereditary coproporphyria (HCP) and not that of NPSLE. All of the symptoms, namely the preceding abdominal pain, the convulsions, fever, hypertension, sinus tachycardia, tetraparesis, and respiratory failure, could be attributed to the AP (Table 1) [2]. The initial attack may have been caused by the use of medication. Valproic acid and calcium channel blockers are candidates for triggering an attack (Table 2) [2]. The clinical course deteriorated by further administration of clonazepam and phenytoin, which are known to be porphyrinogenic drugs.

### Table 1. Clinical manifestations of AP with the estimated incidence [2].

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>85–95</td>
</tr>
<tr>
<td>Vomiting</td>
<td>43–88</td>
</tr>
<tr>
<td>Constipation</td>
<td>48–84</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5–12</td>
</tr>
<tr>
<td>Pain in extremities, back, chest, neck, or head</td>
<td>50–70</td>
</tr>
<tr>
<td>Paresis</td>
<td>42–68</td>
</tr>
<tr>
<td>Respiratory paralysis</td>
<td>9–20</td>
</tr>
<tr>
<td>Mental symptoms</td>
<td>40–58</td>
</tr>
<tr>
<td>Convulsions</td>
<td>10–20</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>28–85</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36–55</td>
</tr>
<tr>
<td>Fever</td>
<td>9–37</td>
</tr>
</tbody>
</table>

AP: acute porphyria.

### Table 2. Common drugs that are unsafe and safe in patients with porphyria [2].

<table>
<thead>
<tr>
<th>Unsafe</th>
<th>Safe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Insulin</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Narcotic analgesics</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Atropine</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Sulfonamide antibiotics</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Streptomycin</td>
</tr>
</tbody>
</table>

Unsafe Safe
Following the diagnosis of HCP, all porphyrinogenic medication was stopped and hematin was started intravenously [2]. Unfortunately, awaiting possible beneficial response, the patient developed cyclophosphamide-induced leucopenia, making her susceptible to infections. The patient suffered from multiple episodes of ventilator-associated pneumonia and ultimately died due to a Gram-negative sepsis.

Discussion
HCP is one of four types of AP. It is a rare, autosomal-dominant metabolic disorder of the production of heme – the oxygen-binding prosthetic group of hemoglobin. It is characterized by a deficiency of the enzyme coproporphyrinogen oxidase (CPO). Heme synthesis begins in the mitochondrion, proceeds into the cytoplasm, and ends in the mitochondrion (Fig. 1). Without CPO, heme synthesis cannot progress, and the metabolite porphyrin accumulates in the cytoplasm, which is toxic. Accumulation of these metabolites causes the characteristic neurovisceral and/or photosensitizing symptoms. The exact mechanism leading to these symptoms remains unclear. Even with the genetic disorder, in unchallenged conditions there still is a 50% CPO enzyme activity, which is sufficient to prevent an acute attack of porphyria. However, infections, certain hormones and drugs, and dietary changes can trigger an attack of AP by inducing the synthesis of cytochrome P450, which consequently increases the heme oxygenase activity. This leads to an abnormal accumulation of the toxic porphyrins. The most common known drugs that can trigger AP are anti-epileptic drugs such as valproic acid, phenytoin, and clonazepam, which were administrated to our patient.

Treatment of mild AP attacks consists of a high carbohydrate diet or a glucose 10% infusion (≥300 g daily), which reduces the activity of heme oxygenase. In severe AP attacks, hematin must also be given intravenously at a dosage of 3–4 mg/kg per day for ≥4 days [2,3]. These are not curative drugs, but they can shorten attacks and reduce the intensity of an attack by inhibiting ALA synthase and thus the accumulation of toxic precursors. Side effects are rare but can be serious, for instance severe coagulopathy and anaphylactic reactions. Discontinuing porphyrinogenic drugs is essential. As many anti-epileptic drugs exacerbate this condition, the treatment of convulsions in these patients is difficult. Some benzodiazepines are safe, and, when used in conjunction with gabapentin, offer a possible regimen for convulsion control [2,4].
Several reports have described the co-appearance of (cutaneous) porphyria in patients with SLE [5,6]. Allard et al. even describe a high prevalence of presence of ANA in patients with AP [6]. However, this appears to be an unfortunate coincidence rather than a specific pathophysiological relationship. As the most common symptoms of AP (abdominal pain, vomiting, tachycardia, and fever) are not especially specific, and because SLE was a likely cause of the neurological symptoms in this case, porphyria was not initially considered in this patient. Many symptoms could be attributed to an active NPSLE. Indeed, the lack of new lesions on a cerebral MRI does not exclude an active NPSLE [7]. However, the poor response to high-dose immunosuppressive therapy, and the electromyography that was not consistent with typical GBS, should have triggered suspicions of an alternative, even more rare, diagnosis, at an earlier stage. The patient might still have responded to the treatment of AP; however, in the meantime the NPSLE treatment had made her even more vulnerable to the infectious complications, which ultimately resulted in her death. AP should be included in the differential diagnosis of atypical NPSLE, especially when presenting with acute neuropathy.

Case Study Editor’s comments
This is a report of the unfortunate result of a missed diagnosis. It highlights that making a differential diagnosis needs to go beyond the obvious and most likely, and should include, even if as a final thought, the rare, the unlikely, and the relatively unknown diseases, especially if the response to treatment is not what may have been expected. It is also an illustration of the hazard of the doctor’s detachment/dissociation from the patient’s bedside. Advanced technical tests may be considered for diagnoses and response to treatment, but in this case, the unusual color of the urine went unnoticed until the patient had a urinary catheter in the ICU. As one of the physicians involved with the care for this patient, I am entitled to be critical. Since this case occurred, we have considered AP and tested for it in two other patients with atypical manifestations of NPSLE. They both tested negative, and the diagnosis of NPSLE was finally confirmed. Given the rarity of AP, I hope that we will not forget this case when the next patient is admitted in several years time.

Disclosures
The authors have no relevant financial interests to disclose.

References
CLINICAL REVIEWS
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

TREATMENT STRATEGIES

Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis

Despite modern therapies, the high mortality rate in patients with systemic sclerosis (SSc; a 5-year mortality rate of 30%) requires the development of novel therapeutic approaches. In the present study, the authors report the results of intensive myelo- and immunosuppression followed by autologous haematopoietic stem cell transplantation to treat severe SSc.

Since 1996, approximately 140 patients with systemic sclerosis (SSc) have undergone haematopoietic stem cell transplantation (HSCT). Early results of Phase I/II clinical trials showed that HSCT is feasible in carefully selected patients with diffuse SSc. A follow-up study of 57 patients revealed a positive response at 3 years in about 66% of the patients with a mortality rate of 8.7% [1]. Based on these data, the present authors initiated an analysis of the long-term follow-up results of the Dutch and French patients from two Phase I/II trials.

The specific aims of this analysis were to evaluate the survival rates and the durability of responses at up to 7 years of follow-up in SSc patients treated with HSCT. A total of 26 patients were followed up. The mobilization and collection of peripheral blood stem cells (PBSC) was performed with 4 g/m² of cyclophosphamide followed by human granulocyte-colony stimulating factor (G-CSF) 4–5 days later. At least 9.5 million CD34+ cells per kg had to be collected by successive daily apheresis to obtain 7 million stem cells after positive selection. Conditioning was performed at least 4 weeks later using cyclophosphamide at 50 mg/kg/day from day –5 to day –2 prior to PBSC injection. To assess the survival and disease response to treatment, clinical evaluation was conducted at least every 6 months. After a median follow-up of 5.3 years (range 1–7.5 years), 81% (21 of 26) of the patients demonstrated a clinically beneficial response. The Kaplan–Meier estimated survival rate at 5 years was 96.2% (95% confidence interval [CI] 89–100%) and at 7 years, 84.8% (95% CI 70.2–100%). The event-free survival rate, defined as survival without mortality, relapse, or progression of SSc resulting in major organ dysfunction, was 64.3% (95% CI 47.9–86%) at 5 years and 57.1% (95% CI 39.3–83%) at 7 years.

This study confirms that autologous HSCT in selected patients with severe diffuse SSc results in sustained improvement of skin thickening and stabilization of organ function up to 7 years after transplantation.


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The comparative one-year performance of anti-tumor necrosis factor α drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study

What is the “survival” of anti-tumor necrosis factor therapy in clinical practice, and what are the predictors of successful long-term use of such therapy? The authors address this question in an observational Norwegian cohort and find that patients with rheumatoid arthritis tend to require a change in regimen sooner than patients with psoriatic arthritis or ankylosing spondylitis. Concomitant methotrexate use was associated with greater longevity of therapy.

Therapy with anti-tumor necrosis factor (anti-TNF) agents is often highly successful in patients with rheumatic illnesses, but...
not all patients remain on therapy in the long-term. Reasons for discontinuation include ineffectiveness and adverse events, among others.

The present group used a Norwegian disease-modifying antirheumatic drug registry to track the course of >1200 courses of anti-TNF therapy to assess factors associated with early discontinuation. They found that the underlying diagnosis was a powerful predictive factor, such that patients with rheumatoid arthritis (RA) had significantly reduced treatment longevity compared with patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS). The crude 1-year drug survival rates were 65.4%, 77.3%, and 77.5% respectively (although the difference between PsA and RA lost significance when adjusted for potential confounders). Among the three drugs (adalimumab, etanercept, and infliximab), etanercept enjoyed the best crude survival rates, but this drug was often the first that was tried, and the survival advantage evaporated when only TNF-naïve recipients were considered. Factors associated with earlier termination of therapy included female gender and higher disease activity. The use of methotrexate correlated with a substantially reduced rate of discontinuation (hazard ratio 0.53; 95% confidence interval 0.43–0.65); no subgroup analysis was presented as to whether this advantage accrued differentially across anti-TNF agents. Interestingly, the methotrexate effect was absent in patients with AS. Improvement in health-related quality of life with TNF therapy was greater in PsA and AS – particularly in the latter, accounting perhaps for the improved duration of therapy in these patients.

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Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial
Rozendaal RM, Koes BW, van Osch GJ et al.

The role of glucosamine in the treatment of osteoarthritis (OA) remains controversial. Only a few studies have investigated its efficacy in hip OA. In this methodologically pristine, 2-year, randomized, double-blind clinical trial free of industry support, patients with hip OA recruited from primary care offices demonstrated no benefit from therapy.

The utility of oral glucosamine for the management of osteoarthritis (OA) remains uncertain, given conflicting results of published clinical trials. Most of these studies have been conducted in knee OA. The present authors designed a clinical trial to assess a therapeutic effect of glucosamine sulfate, 1500 mg daily for 2 years, in patients with hip OA recruited through primary care practices. Patients referred for screening evaluation at the study center were eligible if they met American College of Rheumatology hip OA criteria with Kellgren/Lawrence scores <4 (the most severe), were not awaiting hip surgery, and were not receiving glucosamine therapy. Standardized radiographs were obtained at baseline and 24 months, clinical questionnaires were completed every 3 months, and compliance was assessed by self report and pill counts. Patients and assessors were blinded to the treatment group. Criteria for clinically important changes in pain and function (Western Ontario and McMaster Osteoarthritis Index [WOMAC]) scores, and joint narrowing, were defined in advance.

Out of 417 patients referred from general practitioners, 222 patients with a mean age of approximately 63 years were enrolled in the study. Over 93% were available for final assessment. At 24 months, no significant differences were noted between glucosamine and placebo arms in pain, function, joint space narrowing, or pain medication use; 95% confidence intervals excluded the pre-determined clinically important difference values. Restriction of analysis to patients with excellent (>80%) adherence to therapy did not change these results.

While it remains formally possible that this study missed a clinical subpopulation that responds well to glucosamine – because such patients might already be taking the supplement and would, therefore, be excluded from the trial – the data are extremely convincing that no substantial benefit for hip OA can be expected from glucosamine in the dose regimen assessed.

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Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases
Jais X, Launay D, Yaici A et al.

Connective tissue disease-associated pulmonary arterial hypertension may be successfully managed with a treatment protocol that begins with immunosuppressive therapy and corticosteroids in less severely affected patients, reserving pulmonary vasodilators for those who progress or have severe functional limitations at presentation.
Pulmonary arterial hypertension (PAH) can be a life-threatening complication of various collagen vascular diseases, including progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD). Therapy for PAH has focused on the use of pulmonary vasodilators to counteract vascular hyper-reactivity. However, recent evidence has pointed to the involvement of an immune-mediated inflammatory process in the development and progression of PAH in patients with CTD, suggesting that immunosuppressive therapy may have a role in the management of PAH in at least some of these patients.

In a previous publication, the authors of this manuscript reported on their treatment of a group of patients with PAH related to either SLE or MCTD [1]. They found that a subset of these patients responded to immunosuppressants and glucocorticoids alone, without the addition of pulmonary vasodilators. They proposed that patients who were New York Heart Association functional class I or II, as well as those who were class II but had at least a near normal cardiac index, should be treated with immunosuppressants and glucocorticoids initially, adding vasodilators only if they failed to respond. They also proposed that those patients with worse functional class should be treated with a combination of immunosuppressants, glucocorticoids, and pulmonary vasodilators, although they acknowledged the lack of evidence that the first two were beneficial.

In the current manuscript, the authors report on the first 23 consecutive patients treated according to their proposed algorithm, including 16 who met criteria for treatment with immunosuppressive therapy alone and seven who were treated with a combination of immunosuppressives and vasodilators. Eight of the first group met defined criteria for response (functional class I or II along with hemodynamic improvement at the conclusion of therapy), and six of the eight non-responders subsequently improved with the addition of pulmonary vasodilators. Four of the seven patients in the second group responded to the combination therapy.

The authors conclude that a subset of patients with CTD-associated PAH may respond to treatment aimed at the immune mechanisms presumably responsible for their disease. They propose a sequence of therapy that appears to be successful in their retrospective, uncontrolled series. Randomized, controlled trials in this population will determine whether their approach should become standard of care.


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**Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, Phase IV trial**


Subcutaneous methotrexate (MTX) is clinically more effective than oral MTX in MTX-naïve rheumatoid arthritis patients, although both methods of administration produce substantial clinical benefits in this population.

Low-dose methotrexate (MTX) therapy for rheumatoid arthritis (RA) may be administered orally or via subcutaneous injection. While the latter method is associated with better bioavailability of the medication and has been used for patients with gastrointestinal toxicity from oral dosing, there is uncertainty about whether subcutaneous dosing of MTX generally results in greater clinical efficacy.

In the current study, the authors identified 375 biological agent-naïve patients with active RA randomized to receive 15 mg/week of MTX either orally or subcutaneously, in a blinded fashion for 16 weeks. At week 16, patients who had not achieved an ACR20 response had their dose escalated from 15 mg orally to 15 mg subcutaneously for those originally on oral therapy, and from 15 mg subcutaneously to 20 mg subcutaneously for those originally on subcutaneous therapy. The primary outcome of the study was overall ACR20 response at 24 weeks. Higher levels of response were also assessed.

At week 24, 78% of those initially treated with subcutaneous MTX had achieved an ACR20 response compared with 70% of those initially treated with oral MTX, a difference that was statistically significant. The difference in ACR70 response was also statistically significant at 41% versus 33%, although the difference in ACR50 response was not. Fourteen per cent of the patients, approximately equally split between the two treatment groups, had an escalation of therapy at week 16 after not meeting an ACR20 response. Interestingly, patients with disease duration of >1 year had the highest response to subcutaneous MTX. Overall, adverse events were similar between the two groups; those treated with oral MTX reported more diarrhea, while those treated with subcutaneous MTX reported more loss of appetite.

The authors conclude that subcutaneous MTX is more effective than oral MTX for RA, although the latter certainly appears effective enough to support its initial use if it is more convenient for the patient. The results with both routes of
CLINICAL REVIEWS

administration confirm the effectiveness of MTX as initial monotherapy for RA.

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Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis


On the basis of the ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) study, the present authors validate that patient-reported outcomes for evaluating treatments for rheumatoid arthritis can be used to detect improvements that are important to patients. Physical assessments are more responsive to an effective treatment than psychological assessments.

Patient-reported outcomes (PROs) assess health, wellbeing, and treatment response from the perspective of the patient and may differ from the clinical manifestations. Therefore, the present authors evaluated the responsiveness of PROs, including the Short Form 36-item survey (SF-36), activity limitation, fatigue, and sleep with respect to clinical measures in rheumatoid arthritis (RA) patients. Data were obtained from the ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) study, which evaluated the efficacy and safety of abatacept on a background of disease-modifying antirheumatic drug (DMARD) treatment in patients with active RA who were anti-tumor necrosis factor (anti-TNF) treatment “failures”. Assessments included tender joint count (TJC), health assessment questionnaire (HAQ), and clinical parameters. Multiple PROs including health-related quality of life (measured by the SF-36) and sleep quality were assessed. The ability to detect a treatment effect was evaluated by the treatment difference (abatacept vs. placebo), percentage improvement relative to baseline scores, standardized response mean (SRM), and the relative efficiency for assessing an outcome’s ability to detect a treatment effect relative to the TJC.

The PROs and quality of life (SF-36) indicated great impairment at baseline. The mean changes from baseline in the study outcomes were larger for the abatacept group. The largest relative percent improvements were found for acute phase reactants and the PRO activity limitation, whereas the more psychological PROs (e.g. mental health and mental component score) gave the smallest relative percent improvement. Similar trends could be observed for the SRMs, with a large SRM for physician global, HAQ, SF-36 physician component score, SF-36 bodily pain and fatigue. For the more physical parameters (physician global, SF-36 bodily pain, pain intensity, and HAQ), the relative efficiencies in relation to the TJC for detecting a treatment effect were greater, in contrast to the assessment of psychological components. In general, most of the PROs showed good concordance with both American College of Rheumatology criteria and European League Against Rheumatism response criteria. Significant treatment differences between abatacept and placebo were found for all core set measures and PROs. The differences were substantial in most cases, with significant but smaller differences noted for PROs associated with the more psychological attributes.

GENETICS

The additive effect of individual genes in predicting risk of knee osteoarthritis


Clinically relevant risk factors for osteoarthritis (OA) are obesity, with odds ratios (OR) of 3–18, and knee injury, with OR ranging from 5–16. The OR conferred by genetic risk factors have been found to be small, indicating that genetics is perhaps more relevant in the elucidation of biologically relevant pathways than in disease management. With large-scale genetic testing, this may change. Indeed, the current study indicates some additive effect of individual genetic risk factors in the prediction of risk for OA.

Genetic factors are determinants of osteoarthritis (OA), but most individual genetic associations appear modest. The genotypes for 36 single nucleotide polymorphisms (SNPs) in 17 candidate genes previously associated with OA were analyzed in 298 men and 305 women diagnosed with knee OA, and in 297 male and 299 female control subjects. The odds ratio (OR) for individuals in the top quartile of the “genetic risk” variable, compared with those in the bottom quartile was found to be approximately 9 (95% confidence interval [CI] 5.20–14.49) for women, and about 5 (95% CI 3.10–8.27) for men.

Although these data indicate a relatively large effect, the odds between individuals in the lower versus the upper half of
the distribution according to these known genetic risk factors was only approximately 3. Nevertheless, the fact that additivity of genetic risk factors was observed is encouraging.

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Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX
Hom G, Graham RR, Modrek B et al.

Identification of genetic factors involved in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE) is of obvious importance. In the present study, the authors performed a genome-wide scan of samples from patients with SLE and control subjects in order to identify disease-related genes.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with very strong genetic and environmental components. A number of genes: interferon regulatory factor 5 (IRF5) and signal transducer and activator of transcription 4 (STAT4), and some human leukocyte antigen-DR (HLA-DR) alleles have already been associated with the disease. In this report, the results of a genome-wide single nucleotide polymorphism (SNP) scan in SLE patients and control subjects are described.

A total of 1861 samples from control subjects were genotyped on the Illumina Human Hap550 Genotyping Bead-Chip (Illumina Inc., San Diego, CA, USA). A total of 1465 samples (464 from cases and 1001 from control subjects) were genotyped on the HumanHap550v1 chip, and 1879 samples (1015 from cases and 860 from controls) were genotyped on the HumanHap550v3 chip. An additional, independent set of 1722 samples that were genotyped on the HumanHap550 BeadChip was obtained from public data repositories. Analysis of the genotyped samples was performed in serial phases. After applying the data-quality filters, series one consisted of 411 case subjects and 1047 control subjects, series two consisted of 595 cases and 1516 controls, and series three comprised 305 case subjects and 777 controls. A total of 502 033 SNPs were advanced into analyses. In a replication study consisting of 793 case subjects and 857 control subjects from Sweden, two specific SNPs, namely rs11574637 and rs13277113, were genotyped by the use of fluorescent single-base extension assays. To examine the functional consequences of the finding, the authors analyzed gene expression of B lymphoid tyrosine kinase (BLK) and C8orf13 (chromosome 8p23.1) in B cell lines transformed by the Epstein–Barr virus.

A minor allele of the SNP rs13277113 in the region upstream from the transcription initiation site of the gene encoding BLK and C8orf13 was associated with a risk for developing the disease both in the US and Swedish case–control series (odds ratio [OR] 1.39; p=1x10^{-10}), and also with altered levels of messenger RNA in B cell lines. In addition, variants on chromosome 16p11.22, near the genes encoding integrin alpha M (ITGAM, or CD11b) and integrin alpha X (ITGAX), were associated with SLE in the combined sample (rs11574637; OR 1.33; p=3x10^{-4}). Both associations were confirmed in the replication study.

Thus, two new genetic loci for SLE susceptibility were identified and associated with reduced expression of BLK and increased expression of C8orf13.

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Inhibition of monocyte chemotactrant protein-1 ameliorates rat adjuvant-induced arthritis
Shahrara S, Proudfoot AE, Park CC et al.

The therapeutic inhibition of monocyte chemotactrant protein-1 (MCP-1)/CCL2 and RANTES/CCL5 was examined in rat adjuvant-induced arthritis. Treatment of rats with an inhibitor of MCP-1 (PBA-MCP-1) resulted in amelioration of the disease, whereas inhibition of RANTES or its corresponding receptors (using “AANA”-RANTES and Met-RANTES) had no effect.

The chemokines RANTES/CCL5 and monocyte chemotactrant protein-1 (MCP-1)/CCL2 regulate the chemotaxis of monocytes and T lymphocytes. They are highly expressed in rheumatoid arthritis (RA) synovial tissue and are thought to be involved in the pathogenesis of the disease through the promotion of leukocyte migration into the synovial tissue. In this study, the effects of inhibition of RANTES and MCP-1 were examined in rat adjuvant-induced arthritis (AIA) – an animal model of RA. After the onset of AIA, the modified chemokines PBA-MCP-1 and “AANA”-RANTES, two inhibitors of endogenous MCP-1 and RANTES, respectively, were administered intraperitoneally, separately, or in combination, for 7 or 14 days. Measurement of ankle circumferences and articular index (AI) scores revealed improved clinical signs of AIA after treatment with PBA-MCP-1. Furthermore, PBA-MCP-1 decreased joint inflammation, synovial lining, and bone destruction as
determined by histology, X-rays, and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for the markers associated with bone destruction (receptor activator of nuclear factor-κ ligand and matrix metalloproteinase-9). Downregulation of proinflammatory mediators and a reduction in the number of macrophages in the synovial tissue could be observed by enzyme-linked immunosorbent assay (ELISA) and immunostaining. As RANTES and MCP-1 induce chemotaxis through activation of p38 mitogen-activated protein kinase, the amount of phosphorylated p38 was investigated by immunostaining and Western blot analysis. Reduced activation of p38 was detected in rats treated with P8A-MCP-1. In contrast, treatment with “AANA”'-RANTES had no effect on the evaluated features. Furthermore, the combination of P8A-MCP-1 and “AANA”'-RANTES was not more effective than P8A-MCP-1 alone. Administration of Met-RANTES, an antagonist for RANTES receptors, did not ameliorate clinical signs either.

These results indicate that post-disease onset treatment with P8A-MCP-1 ameliorates AIA. The authors suggest that MCP-1 is critical for the progression of AIA, whereas RANTES may be of limited importance in the pathogenesis of RA.

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Cutting edge: TNFR-shedding by CD4+ CD25+ regulatory T cells inhibits the induction of inflammatory mediators

Regulatory T cells (Treg cells) help to prevent autoimmunity by limiting the activity of other lymphocytes. Recently, experimental evidence in mice has suggested that Treg cells can also limit antigen-independent inflammation. In this article the authors report that activated Treg cells can shed substantial quantities of the tumor necrosis factor (TNF) receptor TNFRII, thereby dampening inflammation driven by innate immune lineages such as macrophages.

Regulatory T cells (Treg cells) represent an important and heterogeneous population of lymphocytes that are capable of blocking the action of other lymphocytes through direct contact as well as production of soluble mediators, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). In general, these cells have been regarded as a “brake” on adaptive immunity, while leaving innate immune cells such as neutrophils, macrophages, and mast cells largely alone. However, this group reports a novel mechanism by which Tregs could impact upon the effector arm of the immune system as well. In this article, they show that Tregs express high surface levels of the p75 tumor necrosis factor receptor TNFRII, the same molecule that forms the TNF-binding site of etanercept. Upon activation, Treg cells begin to shed this receptor via cleavage of the extracellular portion of the molecule, which then binds soluble TNF to prevent it from reaching its targets on the surface of other cells. In a functional assay, the authors show that Treg cells derived from mice deficient in TNFRII lack the ability to antagonize TNF. Further, pharmacological blockade of the enzyme responsible for cleaving TNFRII from the surface results in excess accumulation of this receptor on the surface of Treg cells.

No in vivo data are shown to demonstrate the importance of TNFRII release by Treg cells in inflammatory diseases. Nevertheless, the authors introduce a compelling potential mechanism by which Treg cells could limit autoimmunity at the level of tissue inflammation and injury, in addition to their critical role in the maintenance of self-tolerance.

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A followup study of antiphospholipid antibodies and associated neuropsychiatric manifestations in 137 children with systemic lupus erythematosus

Antiphospholipid (aPL) antibodies can induce neurological disease via cerebrovascular thrombosis and potentially other mechanisms. The present authors investigated the association of aPL antibodies with neuropsychiatric systemic lupus erythematosus (SLE) in 137 children. Anti-β2-glycoprotein I antibodies were somewhat more common among patients with neuropsychiatric SLE, and lupus anticoagulant was found at an elevated frequency in patients with stroke.

The pathogenesis of neuropsychiatric manifestations of systemic lupus erythematosus (SLE) remains uncertain. Since antiphospholipid (aPL) antibodies may have neurological effects above and beyond the promotion of cerebrovascular thrombosis, this group examined a cohort of children with SLE tested regularly for these antibodies for a potential association between aPL and neuropsychiatric lupus. Of 175 patients seen at the Toronto Pediatric Lupus Clinic (The Hospital for Sick Children, Toronto, ON, Canada), 137 met the entry criteria of aPL testing within the first 3 months after diagnosis and longitudinal follow-up within the clinic.
Overall, 66% of children had aPL antibodies at presentation, including anticardiolipin (aCL) in 65%, anti-β₂-glycoprotein I (anti-β₂-GPI) in 41%, and lupus anticoagulant (LAC) in 26%. Approximately 70% of these patients remained persistently positive, while new positives were detected over the course of observation in 20% of the remaining patients (mean follow-up 31 months). Neuropsychiatric SLE was documented in 26% of patients, ranging from headache (the most common) to transverse myelitis. However, evidence for an association between aPL status and neuropsychiatric disease was scarce. Evaluation of potential associations between aPL antibodies (considered individually or collectively, at presentation or over the course of disease) and different neuropsychiatric manifestations identified a plausible association between LAC positivity and stroke (four of five stroke patients compared with 18 of 79 patients without stroke tested for LAC; p=0.015). Anti-β₂-GPI antibodies were positive at some point in 48% of patients with neuropsychiatric manifestations compared with 25% of patients without (p=0.02). Chorea was noted in two patients, both of whom were LAC-positive. General disease activity, as assessed by SLE disease activity index, tended to track with aCL titer but not with anti-β₂-GPI titer.

These findings are of potential interest but, in virtue of the very large number of hypotheses tested in this exploratory study, will require validation in other cohorts.

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INFECTIOUS AND MALIGNANT COMPLICATIONS

Prevalence of malignancy in psoriatic arthritis

Rheumatoid arthritis, particularly when highly inflammatory, has been associated with an increased risk for certain malignancies. These authors examined a prospective registry of >680 patients with adult psoriatic arthritis to determine whether a similar association exists. They found none.

Rheumatoid arthritis (RA) and, potentially, antirheumatic therapies have been associated with a higher risk of lymphoma and potentially certain other malignancies. In addition, psoriasis has been associated with an increased risk for skin malignancy in some studies, although the area remains controversial. To examine whether patients with adult psoriatic arthritis (PsA) develop malignancy at a rate greater than expected for the general population, the authors examined a prospective, well-documented registry of >680 PsA patients for the incidence and nature of first malignancies occurring after entry into the cohort. To capture malignancies not recorded in the registry or after loss to follow-up, the authors queried an Ontario (Canada) cancer registry for data on the same patients. Of 665 patients included in the analysis, 68 (10.2%) developed a malignancy meeting study criteria. Comparison of the risk of malignancy overall, and of common types of malignancy considered separately, showed no change from malignancy incidence in the general Ontario population, as determined through a provincial cancer registry (standard incidence ratio 0.98, 95% confidence interval 0.77–1.24). Patients who developed malignancy did not differ statistically from those without across a wide spectrum of parameters, though use of biologics in the population was limited.

Together the data indicate that PsA, unlike RA, exhibits no clear association with an overall elevated risk of malignancy, but the number of cases was too small to evaluate elevated risk in specific cancer subtypes.

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Morbidity and mortality in rheumatoid arthritis patients with prolonged therapy-induced lymphopenia: twelve-year outcomes

The current armamentarium of drugs against rheumatoid arthritis (RA) consists of agents that modulate the immune system at increasingly sophisticated levels, such as tumor necrosis factor blockade, costimulation blockade, and B cell depletion. Whether such interventions are safe can only be learned from long-term observations. In the early 1990s, patients were treated with the lymphocytotoxic monoclonal antibody alemtuzumab (anti-CD52) with the hope that lymphocyte depletion and reconstitution would result in autoreactive lymphocytes being replaced by a tolerant immune system. In these patients, it was observed that despite continued lymphopenia >11 years after therapy, no excess mortality or unusual infection-related morbidity occurred. These data are reassuring for the long-term outcomes of current immunomodulatory therapies for RA.

In an analysis of 53 rheumatoid arthritis (RA) patients treated with the lymphocytotoxic monoclonal antibody
Hematologic malignant neoplasms after drug exposure in rheumatoid arthritis

Bernatsky S, Clarke AE, Suissa S.


Hematological malignancies seem to occur more frequently in patients with rheumatoid arthritis (RA). However, it is unclear whether there is a link with disease-modifying antirheumatic drug (DMARD) exposure. In a large, case–control study of 619 cases (RA plus hematological neoplasms) and 6190 controls (RA alone, approximately matched in terms of disease severity but without hematological neoplasms) the greatest relative risk (about 2.2) for hematological malignant neoplasms was noted after use of cyclophosphamide. The only other significant risk ratios (RR) were for azathioprine use although this was marginal (the 95% confidence interval was 1.01–2.03). No increased RR were found for the use of methotrexate or antimalarial agents.

This case–control study involved subjects from a cohort of 23 810 patients with rheumatoid arthritis assembled from administrative databases covering the population of the state of Quebec, Canada, in the period 1980–2003. Cases that had hematological malignant neoplasms were ascertained from physician billing and hospitalization records. Patients were matched for age and sex with 10 control subjects and clinical variables and concomitant medications were taken into account, in order to diminish the possibility that the underlying disease led to hematological malignancies. During the study, hematological malignant neoplasms developed in 619 patients, including lymphomas in 346 patients, leukemia in 178 patients, and multiple myelomas in 95 patients. Owing to the fact that biological agents first appeared in Quebec in 2002, there were too few exposures to these drugs to obtain meaningful data.

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The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom

Smitten AL, Choi HK, Hochberg MC et al.


Analysis of US and UK databases shows an increased risk of herpes zoster in rheumatoid arthritis patients, which is further increased with the use of disease-modifying antirheumatic drugs or corticosteroids.

Assessing and quantifying the underlying risk of specific infections in rheumatoid arthritis (RA) is essential to understanding the added risk that may be attributable to disease-modifying antirheumatic drug (DMARD) therapy in these patients. While herpes zoster has been suggested to be more common in patients with RA, the evidence for this is limited, as is any firm evidence linking specific RA therapies to an increased risk of herpes zoster. In the current cohort study, the authors use data from a US managed-care database (PharMetrics claims database) and the UK General Practice Research Database (GPRD) to examine the rate of herpes zoster. The PharMetrics database included 122 272 patients with RA between 1998 and 2002, and the GPRD included 38 621 RA patients from 1990–2001. Compared with non-RA patients, the adjusted hazard ratio for herpes zoster was 1.91 in the PharMetrics database and 1.65 in the GPRD, both of which had 95% confidence intervals that did not cross 1.

Using nested, case–control analysis the authors were able to show that treatment was associated with herpes zoster in both databases. In the PharMetrics database, current use of both biological and non-biological DMARDs alone was associated with a statistically increased risk of herpes zoster, with odds ratios (ORs) of 1.52 and 1.34, respectively. The combination of biological and traditional DMARDs was also associated with increased risk, although this was not statistically significant, possibly because the number of subjects on both therapies was too low. In the GPRD, which did not include any patients taking biological DMARDs, the use of non-biological DMARDs was associated with a statistically increased risk of herpes zoster (OR 1.27). Oral corticosteroid use increased the risk of herpes zoster in both databases, regardless of DMARD use.

These data from two large databases suggest that RA is independently associated with an increased risk for the...
development of herpes zoster, and that this risk may be magnified by the use of corticosteroids, as well as both biological and non-biological DMARDs. This suggests that RA patients may be candidates for the zoster vaccine, which may be particularly appropriate early in the disease course before initiation of therapies that may preclude the use of live vaccines.

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CARDIOVASCULAR RISK

Accumulation of coronary artery disease risk factors over three years: data from an international inception cohort


Risk factors for coronary artery disease (CAD) are present in one-third of patients with systemic lupus erythematosus (SLE) at the initial presentation of the disease, and increase greatly during its early phase. Therefore, patients need to be carefully monitored for proper management of CAD risk factors, from the diagnosis of SLE.

Coronary artery disease (CAD) affects up to 10% of patients with systemic lupus erythematosus (SLE) and CAD risk factors are predictive of myocardial infarction, adverse renal outcomes, and mortality in SLE patients. Therefore, the present investigators monitored CAD risk factors in SLE patients during the early phase of the disease, i.e. during the first years after the diagnosis. A total of 278 patients from the Systemic Lupus International Collaborating Clinics (SLICC) registry (a multicenter, international, inception cohort of newly diagnosed SLE patients) were followed-up over a 3-year period for their clinical, laboratory, and CAD risk factors, which were documented at enrolment and annually.

The SLE patients included in the study were representative of the total SLICC cohort of 935 patients in terms of their demographic features, CAD risk factor differences, and medications. The remaining patients from the cohort had not yet completed 3 years of follow-up. At enrolment, almost one-third of the patients had some classical CAD risk factors such as hypertension (39.2%), hypercholesterolemia (36.3%), or ever smoking (37.4). Over the 3 years of follow-up, all classical CAD risk factors increased by up to 60% of levels at enrollment: 48.6% for hypertension, 65.3% for hypercholesterolemia, 36.7% for smoking, 55.6% for diabetes, and 37.2% for post-menopausal state. Similarly, non-traditional CAD risk factors, present in up to 30% of patients at enrolment, accumulated over the 3 years of follow-up: body mass index increased by 54.3%, waist:hip ratio >0.8 by 79.5%, low physical activity by 71.6%, family history of CAD by 40.8%, and nephrotic syndrome by 82.8%. The Framingham 10-year risk profile was higher in men than in women with SLE both at entry and at 3 years. It decreased in men over the 3-year observation period and remained constant in women. With regard to the use of medications, the treatment of hypertension and hypercholesterolemia, and the use of antimalarials and immunosuppressives increased over 3 years, whereas corticosteroid use increased only slightly.

The authors conclude that CAD risk factors accumulate in SLE patients from the early stages of the disease. Thus, they require careful monitoring, starting at diagnosis, in order to be properly managed.

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Rheumatoid arthritis is associated with a high prevalence of hypothyroidism that amplifies its cardiovascular risk


Hypothyroidism has been linked to an increased risk of cardiovascular disease (CVD), as has rheumatoid arthritis (RA). In the cohort of RA patients investigated by these authors, hypothyroidism was found to be more prevalent than expected, and patients with both RA and hypothyroidism appeared to be at an elevated risk for CVD. The results are thought-provoking but arise from a small sample and will require replication before definitive conclusions can be drawn.

Hypothyroidism has been identified in some studies as a cardiovascular risk factor, operating via factors such lipid profile, blood pressure elevation, and effects on the endothelium. These authors examined a prospective cohort of 358 rheumatoid arthritis (RA) patients for the prevalence of hypothyroidism and its potential effect on cardiovascular disease (CVD) in a population already at an elevated risk because of RA. They found that 6.8% of patients had “clinical hypothyroidism” (defined as an established physician diagnosis of hypothyroidism or the satisfaction of a published criteria set), in excess of the 2.7% expected for the Dutch population in general (p<0.001). Of these 16 women, six (37.5%) had CVD, defined to include either coronary, cerebrovascular, or peripheral vascular disease,
Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus?


During the last decade, a dramatic increase in the incidence of coronary heart disease (CHD) has been observed in patients with systemic lupus erythematosus (SLE). In this retrospective study, it was observed that recent use of corticosteroids and recent lupus activity are independently associated with higher values for several well-recognized CHD risk factors and with overall 2-year CHD risk. These data indicate that novel steroid-sparing drugs should be indicated in the care of SLE patients.

The pathogenesis of the markedly elevated risk of coronary heart disease (CHD) in systemic lupus erythematosus (SLE) patients is unknown. In particular, the causal roles of corticosteroid therapy and SLE disease activity, and whether their putative effects are mediated through conventional risk factors, are unclear. To this end, data were obtained from the charts of >11 000 visits made by 310 patients with SLE to the Montreal General Hospital, Montreal, QC, Canada. A higher past-year corticosteroid dose was independently associated with a significantly higher overall 2-year CHD risk. Moreover, corticosteroid use was associated with higher levels of conventional risk factors such as total serum cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, apolipoprotein B (ApoB), triglycerides, systolic blood pressure (BP), body mass index, and blood glucose. Higher past-year lupus disease activity was also independently associated with higher overall 2-year CHD risk. Furthermore, it was associated with lower HDL cholesterol levels, and higher values for systolic BP, ApoB, triglycerides, and blood glucose.

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Immunologic markers as potential predictors of systemic autoimmune disease in patients with idiopathic scleritis


Scleritis is a painful inflammatory condition of the eye that can be infectious, idiopathic, or secondary to autoimmune conditions such as rheumatoid arthritis and Wegener’s granulomatosis. The authors investigated the utility of testing for rheumatoid factor and antineutrophil cytoplasmic antibody in patients referred to a university-based referral clinic, and found that both tests performed well.

Scleritis manifests as a painful red or purple discoloration of the sclera, and can progress to sight-threatening scleral necrosis. Causes include infections such as herpes and syphilis as well as autoimmune diseases such as rheumatoid arthritis (RA), Wegener’s granulomatosis (WG), and lupus. The present authors conducted a retrospective review of 119 scleritis patients seen at a university clinic, of whom 91 had no evident cause at initial evaluation. Over subsequent follow-up, 11 of these 91 patients were diagnosed with RA and five with WG. Since the general procedure in the clinic was to assess both rheumatoid factor (RF) and antineutrophil cytoplasmic antibody (ANCA), the authors were able to review the predictive value of these tests for the subsequent development of disease. Of the 70 patients tested for RF, 19 (27%) were positive, of whom 10 went on
to receive a diagnosis of RA, whereas only one of 51 RF-negative patients did so. Thus, the positive predictive value of RF in this setting was 52.6%, with a negative predictive value of 98%. RF was predictive even among patients who reported no joint symptoms. ANCA testing was performed in 70 patients and was positive in seven, of whom three developed WG. Two ANCA-negative patients also developed WG, giving positive and negative predictive values of 42.9% and 96.8%, respectively.

The authors conclude that both tests are useful in this clinical setting, but caution that the prevalence of RA and WG may be lower in non-tertiary-care clinics, changing the test characteristics. Whether these tests would provide similar benefits for patients seen in a rheumatology office, where clinical skills in the global assessment for RA and WG are presumably more advanced than in an ophthalmology office, remains an open question.

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High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study
Syversen SW, Gaarder PI, Goll GL et al.

Prediction of joint damage is important for helping the clinician in terms of guiding treatment decisions. In a cohort study from Norway in which follow-up of 125 patients was available for 10 years, the presence of autoantibodies (anti-cyclic citrullinated peptide [anti-CCP] and immunoglobulin M rheumatoid factor), erythrocyte sedimentation rate, and female gender were independent predictors of radiographic progression. Interestingly, the patients with high levels of anti-CCP were especially prone to radiographic progression, indicating that the anti-CCP levels may add more information than the mere presence of anti-CCP.

A cohort of 238 patients with rheumatoid arthritis (RA) was followed longitudinally for 10 years. For 125 of the patients, radiographs of the hands were available both at baseline and after 10 years. Baseline sera were analyzed for C-reactive protein, erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide (anti-CCP), immunoglobulin A rheumatoid factor (IgA RF), and IgM RF. Anti-CCP (OR 4.0) was the strongest independent predictor of radiographic progression. Female gender (OR 3.3), a high ESR (OR 3.2), and a positive IgM RF (OR 3.1) were also independent predictors. Patients with low levels of anti-CCP (OR 2.6) and patients with high levels of anti-CCP (OR 9.9) were more likely to develop radiographic progression than patients with no anti-CCP antibodies. No independent effects were observed for IgA RF, whereas after stratification for ESR it was suggested that an additional effect was observed for RF and anti-CCP antibodies.

Development and validation of a patient-based disease activity score in rheumatoid arthritis that can be used in clinical trials and routine practice
Choy EH, Khoshaba B, Cooper D et al.

Patient-based disease activity scores, either with or without the inclusion of a sedimentation rate, correlate with the 28-joint Disease Activity Score (DAS28) and may be useful both in clinical trials and clinical practice.

As the evidence grows to support the value of objective disease activity measures in rheumatoid arthritis (RA), patient-based disease activity scoring systems, once the province of clinical trials, are increasingly being used in clinical practice. In practice, the acceptability of these measurements may be limited by the perception that their complexity limits the ease with which they can be incorporated into routine patient management. However, in clinical trials the key limitation of these measurements is the high degree of interobserver variability. While this can often be addressed using a single clinician to score disease activity, this solution may be impractical in many situations.

In this paper the authors describe the development and validation of data for an RA disease activity score that is driven by the patients’ own assessments, a method that would address both the complexity and interobserver variability concerns. They developed two patient-based disease activity scores, one with (PDAS1) and one without (PDAS2) a sedimentation rate. Both include the patients’ own assessments of swollen and tender joints, as well as visual analogue scales for pain and general health and a health assessment questionnaire (HAQ).

The PDAS1 and the PDAS2 correlated well with the DAS28 in both the development cohort of 204 patients and the validation cohort of 322 patients. The PDAS1, PDAS2, and the DAS28 all showed similar sensitivity to change, although there was a floor effect with the two PDAS scores, suggesting a decreased sensitivity to change at lower levels of disease activity.

The authors conclude by suggesting that these measurements may have utility in clinical trials,
epidemiological studies, and clinical practice. They suggest that these scores may be particularly valuable in the last case by involving patients in the assessment of their own disease, an important factor in optimizing care. The one caveat the authors note in the use of these scores is that they may not be accurate in detecting remission or near-remission.

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Differences in synovial tissue infiltrates between anti-cyclic citrullinated peptide-positive rheumatoid arthritis and anti-cyclic citrullinated peptide-negative rheumatoid arthritis

The authors of this study analyzed and compared synovial tissue infiltrates from patients with rheumatoid arthritis (RA) who were anti-cyclic citrullinated peptide (anti-CCP)-positive with those from anti-CCP-negative RA subjects. The results demonstrate differences in synovial tissue infiltrates from patients with anti-CCP-positive versus anti-CCP-negative disease, particularly with regard to lymphocyte infiltration.

Anti-cyclic citrullinated peptide (anti-CCP) autoantibodies – highly specific serological markers for rheumatoid arthritis (RA) – often precede the onset of disease symptoms and are thought to be involved in disease pathogenesis. While the clinical presentation of RA patients with or without anti-CCP antibodies is similar at baseline, the progression to erosive disease occurs predominantly in anti-CCP-positive patients. Since only sparse information is available on the pathological features of synovitis in anti-CCP-positive compared with anti-CCP-negative patients, evaluation of synovial tissue infiltrates might help to clarify the role of anti-CCP antibodies in synovial inflammation.

In this basic science study, synovial tissue specimens obtained from inflamed knee joints of 57 RA patients (34 anti-CCP positive, 23 anti-CCP negative) who underwent arthroscopy were analyzed for several histological features along with immunohistochemistry by two independent observers. In addition, standard anteroposterior (AP) knee radiographs obtained within 3 months before or after the synovial tissue sampling were scored for the severity of joint damage using the Kellgren/Lawrence (K/L) scale (range 0–4).

Synovial tissue samples from anti-CCP-positive patients revealed a higher number of infiltrating lymphocytes (61.6 vs. 31.4 cells/high-power field [hpf]; p=0.01) expressing more CD3, CD8, CXCL12, and CD45RO. The difference in the mean number of infiltrating lymphocytes remained demonstrable after correction for disease activity using the 28-joint count disease activity score (DAS28). While there was no difference in vascularity, anti-CCP-positive patients showed a thicker synovial lining layer (mean score 2.1 vs. 3.3; p=0.002) and a decreased extent of fibrosis (mean score 1.2 vs. 2.0; p=0.04). No difference in absolute K/L scores between the groups was observed, but more anti-CCP-positive patients had a K/L score of >1. The evaluation of synovial tissue of 31 patients (18 anti-CCP positive) obtained at earlier time points (mean of 3.8 years before the index biopsy) revealed that the difference in the mean lymphocyte counts was also present at the time of the earlier arthroscopy, with 76.7 cells/hpf in anti-CCP-positive patients compared with 26.7 cells/hpf in anti-CCP-negative patients (p=0.008).

The authors concluded that inflamed synovial tissue in anti-CCP-positive RA patients is different from that in anti-CCP-negative patients, particularly with respect to infiltrating lymphocytes, and shows a higher rate of local joint destruction, which together might reflect differences in underlying pathophysiological mechanisms.

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The Annual European League Against Rheumatism (EULAR) Congress attracts rheumatologists from all over the world and this year >13 000 delegates attended the meeting in Paris, France. A total of 3435 abstracts were submitted for review for presentation at the congress, representing a 9% increase from 2007, and reflecting a continued interest in clinical and scientific research in the field of rheumatology. A wide range of topics was covered at the Congress; this report discusses a few of the key presentations.

Remission in rheumatoid arthritis
A number of presentations demonstrated that remission is an achievable goal in a significant proportion of rheumatoid arthritis (RA) patients. Diane van der Woude (Leiden University Medical Center, Leiden, The Netherlands) presented data on disease-modifying antirheumatic drug (DMARD)-free disease remission, and independent predictors for achieving such remission, in patients at the Leiden Early Arthritis Clinic [1]. During an average follow-up of 8.2 years and a total of 3817 patient-years, 69 of 454 patients (15.2%) with recent-onset RA achieved DMARD-free remission, defined as persistent (>1 year) absence of synovitis without concurrent use of DMARDs. Independent predictors for the achievement of DMARD-free remission included old age, low body mass index, low erythrocyte sedimentation rate, non-smoking, and the absence of anticyclic citrullinated peptide antibodies.

Another group of investigators from The Netherlands performed a prospective study involving a cohort of DMARD-naïve, recent-onset RA patients in daily clinical practice [2]. Patients were treated using a step-up, tight-control approach with methotrexate, followed by sulfasalazine, with adalimumab added to methotrexate at week 24 if remission (28-joint Disease Activity Score [DAS28] <2.6) had not been achieved. The estimated median time to first remission in the 169 patients available for the analysis was 25 weeks, with the following percentages of patients in remission: 15.5% at week 8, 22.2% at week 12, 30.7% at week 20, 38.8% at week 24, 52.1% at week 36, and 51.0% at weeks 48–52.

One-year results from the COMET (Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis) trial were presented by Professor Paul Emery (University of Leeds, Leeds, UK) [3]. This is the first major clinical trial in patients with RA to use DAS28 remission as an endpoint, and involved patients with early, moderate-to-severe, active RA (DAS28 ≥3.2) who had not previously used methotrexate. Subjects were randomized to methotrexate alone (n=268) or methotrexate plus etanercept 50 mg/week (n=274). At 1 year, 50% of etanercept plus methotrexate recipients achieved remission (DAS28 <2.6) compared with 28% of those who received methotrexate alone (p<0.001). In addition, a greater proportion of patients in the combination therapy group achieved low disease activity (DAS28 ≤3.2, 64% vs. 41%; p<0.001). Radiographic non-progression was achieved in 80% of etanercept plus methotrexate recipients and 59% of the methotrexate-only group (p<0.001). Rates of severe adverse events were similar between the two treatment groups. These trial results have subsequently been published in the Lancet [4].

An interim analysis of a German, 5-year, multicenter, prospective study of the efficacy and safety of adalimumab in the setting of day-to-day rheumatology practice was presented [5]. A total of 4640 patients with long-standing RA (mean disease duration 12 years) were included at baseline. After 24 months of adalimumab therapy (data for 824 patients were available), 20% of patients were in clinical remission (DAS28 <2.6) and considerable improvements in physical function were also achieved. Adalimumab was generally well-tolerated among these patients.

The multicenter trial, BeSt (Behandel Strategieen), addressed the effect of tight control of disease with the aim of determining the optimal treatment strategy for early RA patients. Five-year data from this investigation were presented by Dr Naomi Klarenbeek (Leiden University Medical Center) [6]. Longitudinal data analysis showed that those treated with an initial combination of methotrexate and infliximab had significantly better Health Assessment
Questionnaire scores, and a slightly higher drug-free remission rate at 5 years, compared with those who received sequential monotherapy or step-up combination therapy regimens.

Safety of anti-TNFs

Etanercept

The safety of long-term etanercept use was assessed in an analysis of patients with DMARD-refractory RA or early RA who were enrolled in open-label extensions of double-blind, controlled trials in Europe and North America [7]. The results were based on a total of 2054 patients and 9763 patient-years of etanercept exposure, with 57–71% and 35–43% of patients estimated to be continuing on etanercept at 3 years and 9 years (in ongoing North American studies), respectively. The overall rates of severe adverse events in the RA patients were similar to the severe adverse event rates in control patients from the double-blind phase of the included randomized controlled clinical trials. The overall rates of serious infections were similar to those seen in control/methotrexate-treated patients in earlier trials. The standard incidence ratio (SIR) for malignancy was 0.98 (95% confidence interval [CI] 0.78–1.22), calculated using matched data from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database; however, the SIR for lymphoma was 3.53 (95% CI 1.82–6.16). The researchers stated that “it is currently unknown if the higher-than-expected rate of lymphoma is related to TNF antagonist exposure or if it reflects the elevated risk of lymphoma in patients with RA”.

The risk of malignancy associated with etanercept therapy in RA was also investigated by Eric Matteson (Mayo Clinic, Rochester, MN, USA) and colleagues, who presented a meta-analysis of randomized controlled trials [8]. From a total of 3316 patients, 2233 received etanercept and 1072 received control therapy. Malignancies were detected in 26 etanercept recipients and in seven controls, resulting in a hazard ratio for malignancy of 1.84 (95% CI 0.79–4.28), suggesting an increased risk of malignancy in etanercept-treated patients. However, this was not statistically significant and the authors concluded that the small number of cancers precluded their ability to reach definitive conclusions.

An analysis of RA patients included in a German biologicals register assessed the use of biological agents in daily rheumatology practice in patients with a history of cancer [9]. The investigators found that patients received biological agents irrespective of prior malignancies, and the time elapsed since the onset of the malignancy. The rate of malignancy recurrence was similar in patients treated with biological agents and in those who received traditional DMARD therapy.

Adalimumab

ReAlise (A Five-Year, Post-Marketing Observational Study to Follow-up Patients with Rheumatoid Arthritis Formerly Treated in Study M02-497 [ReAct] and Subsequently Prescribed Humira) was undertaken to evaluate the long-term safety and effectiveness of adalimumab for up to 5 years in patients with RA who had previously participated in ReAct (A Study to Assess the Safety and Efficacy of Adalimumab when Added to Inadequate Standard Anti-Rheumatic Therapy in Patients with Active Rheumatoid Arthritis) [10]. An interim analysis of ReAlise was presented by Gerd Burmester (Charité University Hospital of the Free University and Humboldt University of Berlin, Germany) [11]. Data were available for 3421 patients. The rapid initial clinical improvements with adalimumab treatment observed in the ReAct study were sustained in ReAlise. Overall, 11.7% of patients (n=400) withdrew from the study, 4.0% for adverse events and 5.7% for lack of efficacy. No new safety signals were observed in this interim analysis, and the rates of serious infections were low. The SIR, using the SEER database for comparison, was 0.89 (95% CI 0.68–1.13) for all malignancies; however, similarly to that described above for etanercept, the SIR for malignant lymphoma was 3.81 (95% CI 1.90–6.81).

An open-label extension of ATLAS (Adalimumab Trial Evaluating Long-term Efficacy and Safety for Ankylosing Spondylitis), presented by Desireé van der Heijde (Leiden University Medical Center), demonstrated that the statistically significant reduction in AS signs and symptoms (20% improvement in Assessment in Spondyloarthritis international Society criteria) observed at 24 weeks (in the double-blind phase) was sustained at up to 3 years of treatment [12]. Comparison of adverse events and severe adverse events rates between the double-blind and 3-year exposure periods, identified no significant differences between the two treatment periods. In addition, there were no cases of tuberculosis or demyelinating disorders.

Data on radiographic progression in patients entered into an open-label extension of the 24-week, Phase III trial, ADEPT (Adalimumab Effectiveness in Psoriatic Arthritis Trial), were presented by Philip Mease (Seattle Rheumatology Associates, Seattle, WA, USA) [13]. In initial adalimumab responders in the ADEPT study, continued treatment with open-label adalimumab led to sustained inhibition of radiographic progression at up to 144 weeks.

Novel agents

Golimumab

Data from Phase III trials of the anti-TNF antibody, golimumab, were presented at the Congress. The results of GO-FORWARD (Golimumab for Subjects with Active RA
Despite methotrexate), presented by Edward Keystone (Toronto University, Toronto, ON, Canada), showed that golimumab plus methotrexate was significantly more efficacious than methotrexate alone in subjects with active RA [14]. In GO-AFTER (Golimumab after Former anti-TNF Therapy Evaluated in RA), 461 patients with active RA who had previously received at least one anti-TNF agent (65% had failed one, 25% failed two, and 10% failed three) were randomized to placebo, golimumab 50 mg subcutaneously, or 100 mg subcutaneously every 4 weeks. Josef Smolen (University of Vienna, Vienna, Austria) presented data from the study [15]. Prior anti-TNF therapy had been discontinued due to lack of efficacy in approximately 60% of patients. Among this subgroup, 35.7% and 42.7% of patients in the golimumab 50 mg and golimumab 100 mg groups had a 20% improvement in American College of Rheumatology criteria (ACR20) response at week 14 compared with 17.7% of the placebo group (p=0.006 and p<0.001, respectively). Adverse event and severe adverse event rates were similar across the treatment groups. This study is the first to demonstrate that a patient who fails on up to three anti-TNF-α agents may be successfully treated with another.

Arthur Kavanaugh (University of California–San Diego, La Jolla, CA, USA) presented data from GO-REVEAL (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Golimumab, a Fully Human Anti-TNF-α Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Psoriatic Arthritis) [16]. Golimumab was significantly more efficacious in improving the signs and symptoms of psoriatic arthritis (PsA) at week 24 compared with placebo, and its efficacy was maintained at week 52. At week 24, 2.4% of golimumab-treated patients experienced severe adverse events compared with 6.2% of placebo recipients. In a separate presentation of data from GO-REVEAL [17], treatment with golimumab significantly improved psoriatic nail changes, dactylitis score, and enthesitis score in patients with active PsA (all p<0.001 compared with placebo).

Tocilizumab

Several Phase III trials of tocilizumab, an anti-interleukin-6 (anti-IL-6) receptor antibody, were presented at this year’s Congress. The AMBITION (Actemra™ [Tocilizumab] versus Methotrexate Double-Blind Investigative Trial in Monotherapy) investigators assessed the efficacy and safety of tocilizumab monotherapy versus methotrexate monotherapy in patients with active RA who had not failed previous methotrexate or biological treatment. Tocilizumab monotherapy (8 mg/kg every 4 weeks) was found to be superior to a standard escalating dose of methotrexate, with higher proportions of patients achieving ACR20, ACR50, and ACR70 responses at week 24 [18]. Professor Graeme Jones (University of Tasmania, Tasmania, Australia) and colleagues also reported safety data from the study. Severe adverse events and serious infections were slightly higher in those treated with tocilizumab compared with methotrexate (4% vs. 3% and 1.4% vs. 0.7%, respectively). In contrast, elevation in liver enzymes occurred more frequently in the methotrexate group than in the tocilizumab arm (4% vs. 2%).

The results of RADIATE (A Randomized, Double-Blind Study of Safety and Reduction in Signs and Symptoms During Treatment With Tocilizumab Versus Placebo, in Combination With Methotrexate, in Patients With Moderate to Severe Active Rheumatoid Arthritis and Inadequate Response to Anti-TNF Therapy) were presented by Professor Emery. Tocilizumab plus methotrexate therapy was demonstrated to be efficacious in the treatment of refractory RA patients, irrespective of the number of, or most recently failed anti-TNF treatment [19].

INCB18424

William Williams (Incyte Inc., Wilmington, DE, USA) and colleagues presented results from a 28-day proof-of-concept trial of INCB18424, an orally available Janus-associated kinase (JAK) inhibitor, in eight patients with active RA [20]. Six subjects received the inhibitor, while two received placebo. Four of the six INCB18424-treated subjects achieved at least an ACR20, three achieved at least an ACR50, and two achieved an ACR90 response. Three patients achieved a DAS28 score <2.6, and the mean DAS28 score decreased from 6.0±0.32 to 3.29±0.99 by day 28. This is the first demonstration of clinical activity of a selective JAK inhibitor in RA.

References


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