Diagnostic and Therapeutic Opportunities in Undifferentiated Arthritis
Annette HM van der Helm-van Mil and Tom WJ Huizinga

Psychological Factors in Rheumatoid Arthritis
Jerry C Parker, Eric S Hart, and Sara Walker

Crohn’s Disease and Spondyloarthropathy
Martine De Vos

Case Study: An Unusual Case of Acute Shoulder Pain
Suresh K Chhetri, Zunaid Karim, and Andrew R Harvey
Faculty Disclosures

Editorial Policy
*International Journal of Advances in Rheumatology* is an independent journal published by Remedica Medical Education and Publishing. Editorial control is the sole responsibility of the Editors-in-Chief, Editorial Advisory Board, and the Editors. Before publication, all material submitted to the journal is subjected to rigorous review by the Editors-in-Chief, Editorial Advisory Board, Editors, and/or independent reviewers for suitability of scientific content, scientific accuracy, scientific quality, and conflict of interest.

Aims and Scope
*International Journal of Advances in Rheumatology* is designed to bring a critical analysis of the world rheumatology literature, written by clinicians, for clinicians, to an international, multidisciplinary audience. Our mission is to promote better understanding of rheumatological medicine across the global healthcare system by providing an active forum for the discussion of clinical and healthcare policy issues.

Leading Articles - These major review articles are chosen to reflect topical clinical and healthcare issues in rheumatology. All contributions undergo a strict editorial review process.

Clinical Reviews - The most important papers from the best of the international literature on rheumatology are systematically selected by an internationally recognized panel of experts. The Editors then prepare concise and critical analyses of each paper, and, most importantly, place the findings into clinical context.

Meeting Reports - *International Journal of Advances in Rheumatology* also provides incisive reportage from the most important international congresses.

Publisher’s Statement
©2007 Remedica Medical Education and Publishing. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior permission of the copyright owners. While every effort is made by the publishers and editorial board to see that no inaccurate or misleading data, opinions, or statements appear in this journal, they wish to make it clear that the material contained in the publication represents a summary of the independent evaluations and opinions of the authors and contributors. As a consequence, the board, publishers, and any supporting company accept no responsibility for the consequences of any such inaccurate or misleading data or statements. Neither do they endorse the content of the publication or the use of any drug or device in a way that lies outside its current licensed application in any territory. *International Journal of Advances in Rheumatology* (ISSN 1478-856X) is published four times a year by Remedica Publishing Ltd and distributed by USA Mail Agent CMM LLC, 147–29 182nd Street, Jamaica, NY 11413. Subscription price $170 per year. Periodicals Postage Pending at Jamaica, NY. POSTMASTER: Please send address changes to Remedica Publishing Ltd, c/o CMM 147–29 182nd Street, Jamaica, NY 11413.

Remedica Medical Education and Publishing Ltd., 20 North Wacker Drive, Suite 1642, Chicago, IL 60606, USA.
Telephone: +1 (312) 372 4020 Fax: +1 (312) 372 0217 Email: info@advancesinrheumatology.com

Editor: Joe Gray Editorial Manager: Scott Millar

ISSN 1478-856X
Diagnostic and Therapeutic Opportunities in Undifferentiated Arthritis

Annette HM van der Helm-van Mil, MD, and Tom WJ Huizinga, MD
Department of Rheumatology, Leiden University Medical Center, The Netherlands

Currently, patients with early rheumatoid arthritis (RA) are treated promptly with disease-modifying antirheumatic drugs. This new treatment paradigm, in combination with new therapeutic options, has already improved the prospects for patients with RA. Nevertheless, the ultimate challenge for the future is to initiate therapy in such an early phase that the actual development of RA is prevented. In this phase, it is plausible that the mechanisms driving chronicity are less established and remission may be induced more easily. Early undifferentiated arthritis (UA) is defined as early arthritis that cannot be classified according to American College of Rheumatology criteria and that is not septic or reactive in origin, and thus is a diagnosis per exclusionem. Early UA is sometimes confounded by early arthritis; however, discrimination of the patient groups is relevant when comparing the outcome of studies. The natural disease course of UA is variable: one-third of patients develop RA and 26–55% achieve a spontaneous remission. To minimize over- and undertreatment of patients with early UA, a model has recently been constructed that estimates the likelihood of progression to RA in individual patients with UA. Int J Adv Rheumatol 2007;5(2):34–9.

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may have a high impact on patients’ quality of life, because it is associated with disability, comorbidities, and an increased mortality rate [1]. In the last 10 years, it has been recognized that RA needs to be diagnosed early and treated promptly with disease-modifying antirheumatic drugs (DMARDs) in order to successfully interfere with the disease process. This new treatment paradigm, in combination with new therapeutic options, has already improved the prospects for patients with RA, with reductions in the levels of joint destruction, disability, and mortality.

While rheumatologists can now successfully reduce the degree of disease activity in patients with RA, the ultimate challenge for the future is to initiate therapy in such an early phase that the actual development of RA is prevented. Clearly, this will require patients to be treated before the disease is fully developed. It is plausible that in an early phase of the disease, the mechanisms that drive chronicity are less established and that interference with the disease process will induce remission more easily. For patients to be treated before the disease is fully developed, rheumatologists require two tools: first, a means of identifying patients who will develop RA; and, second, drugs that are proven to be effective in preventing the development of RA.

It is conceivable that, in the coming years, clinical trials will be designed to assess treatment efficacy in patients with early undifferentiated arthritis (UA). This article appraises the definition of UA, the natural course of UA, clinical characteristics that predict progression from UA to RA, and pathophysiological differences between UA and RA. In addition, findings from the first trial investigating the effect of DMARDs in patients with UA are presented.

Definitions of early arthritis and UA
Trials evaluating treatment strategies for RA include patients classified according to the 1987 American College of Rheumatology (ACR) criteria for RA [2]. These criteria were developed by experts who compared characteristics of patients with longstanding “classical” RA (mean disease duration 8 years). In clinical practice, patients presenting with early arthritis frequently have an undifferentiated disease that may progress to polyarthritis fulfilling the ACR criteria for RA, or they may have a more benign disease course. The ACR criteria have been criticized as they have low discriminative ability in patients presenting with recent-onset arthritis [3–6]. This is not surprising, considering the components of the ACR criteria. One of the criteria is the presence of erosions on radiographs of hands and wrists. However, in the early phases of RA only 13% of the patients...
have erosive disease [7]. Additionally, erosions often initially present in the small joints of the feet and appear in the small joints of the hands at a later point in the disease course [8]. Furthermore, rheumatoid nodules are very rare in the early phases of RA and rheumatoid factor is present in only 50% of patients with early RA [9].

A set of criteria is needed that applies to early UA and that differentiates patients with UA who will progress to RA from those who will have a more benign disease course. As a basis for identifying characteristics that predict disease outcome in patients with UA, it is important to explore the definition of early arthritis and UA.

In the literature, several terms that refer to arthritis of recent onset are used, but they refer to distinct categories of patients and should therefore be separated. The most frequently used terms are “early arthritis,” “early RA,” and “UA.” Early arthritis involves a recent onset of mono-, oligo-, or polyarthritis, and it can be undifferentiated or differentiated. Approximately 20% of patients presenting with early arthritis fulfill the ACR criteria and can thus be classified as having early RA [10]. Since the ACR criteria stipulate that patients must fulfill the conditions for ≥6 weeks, a disease duration of <6 weeks precludes a diagnosis of early RA, by definition. Patients with early arthritis may also fulfill classification criteria for other diagnoses. Finally, those patients with early arthritis who cannot be classified according to ACR criteria and in whom the disease is not septic or reactive in origin have UA per exclusionem.

Discriminating UA from early arthritis and early RA is relevant when comparing studies that describe models predicting disease outcome or studies that assess therapeutic efficacy, because the generalizability of these studies depends on the patient group that is included.

Natural disease course of UA
The natural disease course of UA has been variably reported in a number of inception cohorts. This is not only due to the use of different definitions for UA, but also a result of differences in inclusion criteria for several early arthritis cohorts. For example, inclusion in the UK-based NOAR (Norfolk Arthritis Register) demanded the presence of at least two swollen joints [11], whereas inclusion in an early arthritis clinic in Leeds (UK) and an arthritis cohort from Wichita (KS, USA) did not require the presence of synovitis [12,13]. Furthermore, some early arthritis clinics included only patients who fulfilled the criteria for RA [14,15]. Inclusion criteria for early arthritis cohorts also differ in the required symptom duration. Patients could be included in NOAR when arthritis was present for ≥4 weeks [11], whereas a symptom duration of <12 weeks was an exclusion criterion for an early arthritis cohort from Birmingham (UK) [16].

Early arthritis cohorts that have included all patients with at least one swollen joint have reported that approximately 20% of patients fulfilled the criteria for RA at initial presentation and that 35–54% of the patients presented with UA [17,18]. Among the cases of UA, the disease course was diverse: 40–55% remitted spontaneously [18–21], 35–50% developed RA [7,17], and the remaining patients developed other diagnoses or remained undifferentiated (Fig. 1).

Data from early arthritis cohorts have also illustrated that the duration of symptoms is of importance for the outcome of patients with UA. For instance, in the Leiden Early Arthritis Clinic, only a minority (10%) of patients who had persistent UA after 1 year of follow-up developed RA later on in the disease course.

Intriguingly, the reported rates of spontaneous remission in cases of UA are different from those in cases of RA. Whereas remission has been noted in 40–55% of patients with recent-onset UA, the remission rate in cases of RA is at most 10–15% [22,23]. It seems, then, that the likelihood of a natural remission becomes smaller as the disease process advances. This supports the notion that chronicity might be more easily reversed in the phase of UA.

Predicting progression from UA to RA
Because UA has a variable disease course and DMARD therapy is potentially toxic, a preferential treatment approach would...
be for only the patients with UA who have a high likelihood of developing RA to be treated with DMARDs, with those who will achieve a spontaneous remission not receiving these drugs. This serves as the rationale for a model that is able to predict disease outcome in individual patients with UA.

Initial attempts to define such prognostic criteria have been made by Visser et al., based on the Leiden Early Arthritis Cohort [24]. Their model predicts disease persistency and erosiveness. For the development of this model, all patients with early arthritis were included, not just those with UA. Consequently, patients that at first presentation were classified, for example, as having reactive arthritis or RA were also included. However, the natural course of these diseases is already known: reactive arthritis is generally remitting, while RA is typically a persistent disorder. Including patients with a diagnosis for which the disease course is well known may skew a model that predicts disease outcome.

Therefore, the model of Visser et al. is not optimal in guiding individualized treatment decisions in UA.

Recently, another model based on the Leiden Early Arthritis Cohort has been developed for predicting disease outcome in individual patients with UA [25]. From a total cohort of 1700 patients with early arthritis, 570 presented with UA. After 1 year of follow-up, 31% of the patients with UA had progressed to RA. The remaining two-thirds had either developed other diagnoses (16%) or achieved spontaneous remission (26%), or remained unclassified (26%). Clinical characteristics were compared between patients with UA who had developed RA and those who had not. Logistic regression analysis was used to determine parameters that independently predicted the development of RA. A prediction rule was constructed based on the findings (Tables 1A and 1B) [25].

The discriminative ability of this prediction rule was assessed using receiver–operator characteristic analysis; the area under the curve was 0.89 for the derivation cohort and 0.97 for the replication cohort. The total prediction score ranged between 0 and 14. No patients with a score <4 and all patients with a score >10 progressed to RA. Using cut-off levels of ≤6 and ≥8, the negative and positive predictive values were 91% and 84%, respectively. As this prediction rule consists of nine variables that are regularly assessed at the outpatient clinic (age, sex, distribution of involved joints, etc.), it is feasible to use in clinical practice.

### Table 1A. The form used to calculate the prediction score in points for individual patients with undifferentiated arthritis.

| 1. What is the age in years? Multiply by 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| 2. If female: 1 point | 0.5 | 1 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| 3. If small joints of hands or feet: 0.5 points | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| If symmetric: 0.5 points | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| If upper extremities: 1 point | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| If upper and lower extremities: 1.5 points | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| 4. If 26–90 mm: 1 point | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 |
| If >90 mm: 2 points | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 |
| 5. If 4–10: 0.5 points | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| If ≥11: 1 point | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| 6. If 4–10: 0.5 points | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| If ≥11: 1 point | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| 7. If 5–50: 0.5 points | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| If ≥51: 1.5 points | 51 | 51 | 51 | 51 | 51 | 51 | 51 | 51 | 51 |
| 8. If yes: 1 point | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9. If yes: 2 points | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total score | | | | | | | | | |

CCP: cyclic citrullinated peptide; VAS: visual analogue scale. Published with permission from [25].

### Table 1B. Rate of progression to RA for the different prediction scores.

<table>
<thead>
<tr>
<th>Prediction score</th>
<th>No progression to RA – n (%)</th>
<th>Progression to RA – n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1</td>
<td>8 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>42 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3</td>
<td>58 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4</td>
<td>78 (93)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>5</td>
<td>73 (85)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>6</td>
<td>63 (74)</td>
<td>22 (26)</td>
</tr>
<tr>
<td>7</td>
<td>37 (49)</td>
<td>38 (51)</td>
</tr>
<tr>
<td>8</td>
<td>16 (33)</td>
<td>33 (67)</td>
</tr>
<tr>
<td>9</td>
<td>6 (14)</td>
<td>36 (86)</td>
</tr>
<tr>
<td>10</td>
<td>5 (23)</td>
<td>17 (77)</td>
</tr>
<tr>
<td>11</td>
<td>0 (0)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>12</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>13</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis. Published with permission from [25].
An aggressive disease course.

Short, it might predispose an individual to arthritis or result in antibody production in older people [27]. Immunosenescence is exemplified by the development of a polyreactive (TNF-α), and IL-6 [26]. Modification of the adaptive immune system is exemplified by the development of a polyreactive antibody production in older people [27]. Immunosensenscence is discussed in more detail by Ginaldi et al. [28], but, in short, it might predispose an individual to arthritis or result in an aggressive disease course.

Sex

Sex hormones influence predisposition to autoimmune diseases. In general, men are less prone than women, which might be a result of anti-inflammatory effects of androgens. It was recently demonstrated that the expression of peroxisome proliferator-activated receptor α in CD4+ T cells was sensitive to androgen levels and was greater in males. This increased expression was found to induce higher levels of T helper 2 (Th2) cytokines and consequently a lower susceptibility to Th1-mediated autoimmune diseases [29]. Estrogen has also been shown to suppress arthritis in mouse models [30], and the use of oral contraceptives might be associated with a lower risk of RA development [31]. However, this finding was not replicated in the Nurses’ Health Study [32]. Additionally, both estrogen and androgen inhibit bone resorption [33]. Moreover, sex hormones may have local effects that seem to consist mainly of modulation of cell proliferation and the production of cytokines (i.e. TNF-α and IL-1). Taken together, these data suggest that postmenopausal women exhibit a pro-inflammatory cytokine profile, which might contribute to the higher incidence of RA seen in this population subgroup.

Distribution of involved joints

RA affects the small joints of the hands and feet in particular, whereas large joints are more susceptible to inflammation in some other rheumatological diseases. The reason for this phenomenon is not clear. It has recently been suggested that differential accumulation of regulatory T cells in different joints may dictate the anatomical spectrum seen in arthritis syndromes [34]. However, this hypothesis is based on animal models; whether this might explain the distribution of inflamed joints in humans is not known.

Severity of morning stiffness

Although the presence of morning stiffness is a specific maker for RA in clinical practice, the underlying biological mechanisms require further examination. Straub and Cutolo recently proposed that the symptom of stiffness is due to edema formation mediated by circulating pro-inflammatory cytokines [35]. The observation that levels of the pro-inflammatory cytokines TNF-α and IL-6 exhibit a circadian rhythm and peak at approximately 6:00–7:00 AM in patients with RA might support this hypothesis and explain why stiffness is most severe in the early morning.

CRP level and numbers of tender and swollen joints

IL-6 enhances the hepatic production of CRP, which explains why in situations involving increased levels of IL-6 (e.g. later age and inflammation), levels of CRP are also elevated. More generally, levels of CRP directly reflect the levels of pro-inflammatory cytokines. Additionally, the numbers of tender joints and swollen joints may mirror the level of pro-inflammatory activity. It seems reasonable to suggest that in cases of locally increased pro-inflammatory activity, the biological processes that generate RA are boosted.

Rheumatoid factor and anti-CCP antibodies

The associations between most of the aforementioned factors and RA are, in part, mediated by an increased level of pro-inflammatory cytokines; therefore, they reflect quantitative parameters. The last two items in the prediction model – the presence of two types of autoantibodies – are primarily qualitative. While it is still uncertain whether these autoantibodies are of pathophysiological importance or the result of a bystander effect, the specificity of anti-CCP antibodies for the development of RA has been extensively reported. A recent study revealed that not only the presence of anti-CCP antibodies, but also – in cases of anti-CCP positivity – the level of these antibodies, was correlated with
an increased risk of progressing from UA to RA [36]. Moreover, not only the level but also the nature of the autoantibody response is different in UA and RA. In another study, patients with UA were found to have a lower number of anti-CCP isotypes than patients with RA [37]. Similarly, patients with UA who progressed to RA had a higher number of isotypes than patients with UA who did not develop RA [37].

Outcomes of treatment in UA

To date, only one study has been conducted to assess the efficacy of therapeutic strategies in patients with UA [38]. In this double-blind clinical trial, patients were randomized to treatment with either methotrexate or placebo. Patients were followed for 30 months and both the progression toward RA and the level of joint destruction were measured. A significantly lower number of patients treated with methotrexate than those treated with placebo progressed to RA. In addition, the patients with UA who were treated with methotrexate had a significantly lower level of radiological joint destruction, indicating a less severe disease course. Interestingly, after the cessation of methotrexate at 18 months, the difference in the number of patients who developed RA became smaller but remained statistically significant. This suggests that, in some patients, methotrexate hinders disease progression but does not halt the underlying pathophysiological mechanisms. It is necessary for these data to be replicated in other studies. Nevertheless, the results are promising since they indicate that treatment in an early phase of RA, before the disease is established, is effective. It is hoped that future targeted therapies will be able to fully halt the development of persistent arthritis.

Conclusion

UA is a diagnosis per exclusionem and refers to arthritis that cannot be classified according to current criteria; it is different from “early arthritis” and “early RA.” The disease course of UA is variable and approximately one-third of patients are in an early phase of RA. Patients with UA represent a therapeutic opportunity, because the disease process in UA is less established and treatment in this early phase might halt the progression toward RA. In order to achieve this, physicians will need to be able to predict which patients with UA will progress to RA and to have drugs available that are proven to be effective in UA. A rule that predicts the likelihood of developing RA in individual patients with UA has recently been developed and clinical trials evaluating the effects of DMARD therapy in UA are being designed. It is hoped that physicians will be able to offer personalized medicine within the next 10 years, enabling the impact of arthritis on patients’ quality of life to be further diminished.

Disclosure

The authors have no relevant financial interests to disclose.

References

36. van der Helm-van Mil AH, Verpoort KN, le Cessie S et al. The HLA-DRB1 shared epitope alleles differ in the interaction with smoking and predisposition to antibodies to cyclic citrullinated peptide. *Arthritis Rheum* 2007; 56: 425–32.
Psychological Factors in Rheumatoid Arthritis

Jerry C Parker, PhD1, Eric S Hart, PsyD2, and Sara Walker, MD3
1Dean’s Office, School of Medicine, 2Department of Health Psychology, and 3Department of Internal Medicine, University of Missouri, Columbia, MO, USA

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases in the US. The course of RA is characterized by polyarticular pain and joint inflammation. Although the etiology of RA is still to be fully determined, psychological variables have been found to influence functional status. In general, persons with RA frequently experience emotional challenges in addition to a variety of physical limitations. A sizable percentage of persons experience emotional distress (e.g., pain and depression) during the course of RA. This article reviews the current literature on the psychological variables associated with RA and addresses the outcome research on available treatment options. In general, persons with RA appear to require psychological adaptation to the potentially debilitating physical symptoms and changes in functional status associated with the condition. Overall, the preponderance of evidence justifies a comprehensive biopsychosocial framework for symptom management. Int J Adv Rheumatol 2007;5(2):40–3.

Biological responses associated with stress
In a review of the literature, Rogers and Fozdar reported research evidence to support a relationship between psychological factors and both immune functioning and disease activity in RA [6]. Zautra et al. found that psychological stressors (e.g., interpersonal conflicts and depression) were linked to hormones that stimulate immune function, such as prolactin and estradiol [7]. Walker et al. reviewed studies that suggest that psychosocial stressors in RA are associated with dysfunction of neuroendocrine and immune modulation [8].

Cash and Wilder indicated that many types of stressors can activate the hypothalamic–pituitary–adrenal (HPA) axis [9]. Huyser and Parker reviewed the literature on the role of stress in RA and described the relationship between stress and the HPA axis [10]. Activation of the HPA axis is initiated by corticotropin-releasing hormone secreted from the hypothalamus, which, in turn, results in the pituitary release of adrenocorticotropic hormone (ACTH). By way of the bloodstream, ACTH reaches the adrenal cortex, where
cortisol and other glucocorticoids are released [11]. Cortisol, in particular, has been found to play an important role in inhibiting inflammation. Dysregulation of the HPA axis may contribute to the manifestation of symptoms in RA [9]. For example, Zautra et al. provided general evidence that interpersonal stressors are predictive of increases in disease activity, although not for all persons with RA [12].

Huyser and Parker suggested that major stressors, such as the death of a loved one, appear to result in a decrease of RA symptoms [10]. Conversely, minor stressors appear to produce an increase in disease activity. This paradox of the differential influences of stress on RA disease activity may be associated with the cortisol response. Specifically, major stressors may induce dramatic increases in cortisol that counteract the inflammatory process, whereas minor stressors may result in a more restrained release of cortisol.

**Pain in RA**

The association between pain and disease course in persons with RA remains unclear. Parker et al. found that pain was correlated with age, income, and psychological distress [13]. However, the correlation between pain and medical variables (e.g. sedimentation rate, anatomical stage, disease duration, and joint swelling) was not found to be statistically significant. Fifield et al. found that lower levels of pain and depression were associated with a greater ability to maintain paid employment [14]. Interestingly, they also found that those persons who experienced the greatest level of disease severity did not consistently experience the highest level of pain and depression. In contrast, loss of employment was correlated with higher levels of pain and depression at all levels of disease severity.

Keefe et al. reviewed the literature on the psychological aspects of coping with chronic pain in RA and concluded that poor adjustment to pain was associated with variables such as pain catastrophizing, pain-related anxiety or fear, and feelings of helplessness [15]. Pain catastrophizing, defined as a negative appraisal of one’s ability to manage pain, had the strongest correlation with chronic pain symptoms. In addition, the authors found that persons who scored high on measures of pain-related anxiety or fear had a tendency to overestimate the level of pain that they would experience upon physical examination.

In an examination of the influence of coping strategies on the management of pain in RA [16], Keefe et al. conducted both within- and between-person analyses to determine the relationship between daily coping efficacy, pain coping strategies, incidence of pain, and mood. Interestingly, persons who experienced greater coping efficacy had a tendency to use relaxation exercises, make cognitive attempts at re-defining their pain, and seek spiritual support; increases in coping efficacy were associated with decreases in negative mood.

A history of depression is associated with higher pain intensity, fatigue, and disability during times of dysphoria for persons with RA. Fifield et al. suggested that current symptoms of dysphoria can activate a “scar” that may exist secondary to a history of depression; this activation leads to heightened levels of pain, fatigue, and disability in persons with RA [17]. Conner et al. found that a history of depression was associated with a greater tendency to cope with increased pain by venting emotions. In this study, persons with pre-existing depression perceived that they had less control over their pain during periods of increased distress [18].

**Depression in RA**

Creed and Ash reported the occurrence of depression in approximately 17–27% of persons with RA [19]. Overall, depression occurs more frequently in persons with rheumatic diseases than in those without serious chronic conditions [20]. However, base-rate estimates of depression in persons with RA can be misleading owing to the overlap between the physical symptoms of RA and the somatic symptoms of depression. A meta-analysis conducted by Dickens et al. found that depression was more common in persons with RA than in healthy individuals; the degree of pain was found to be associated with the difference in depression level between these two groups [21]. Within the context of RA, age is an important demographic variable associated with depression. Specifically, younger individuals with RA have a higher risk for developing depression when compared with older individuals; child-rearing responsibilities and job-related stress have been proposed as contributors to depression in younger persons with RA [22]. Covic et al. found that fatigue, pain, and physical disability were the clinical features most strongly associated with depression in persons with RA [23].

The temporal relationship between depressive symptoms and disease course in RA has been given considerable attention in the literature. Newman et al. examined the influence of multiple variables on depression in RA and found that, following diagnosis, depression decreased over time [24]. They indicated that adaptation to the symptoms of RA may be responsible for this temporal decrease of depressive symptoms. Strating et al. studied the longitudinal relationships between RA disease-related factors (e.g. joint tenderness, pain, and functional disability), social support, and distress [25]. They found that the effect of RA disease-related factors on emotional distress decreased over time. Greater satisfaction with both emotional support and social companionship was found to be positively correlated with decreased emotional distress.
Overall, the associations between RA disease activity and psychological well-being are not consistent. Specifically, changes in functional status are not always associated with changes in depressive symptoms for persons with RA [26]. Dickens et al. examined the influence of demographic variables, disease activity, and social stressors on depression in persons with RA [27]. Surprisingly, social difficulties alone differentiated between depressed and non-depressed persons with RA.

Treatment
Psychopharmacological intervention
Although research into psychopharmacological treatment for depression in RA has been limited, existing studies have yielded promising results. Parker et al. found that treatment with the antidepressant sertraline resulted in significant clinical improvement of persons with RA for variables such as depression, helplessness, self-efficacy, psychological distress, perceived life stress, anxiety, coping, fatigue, and aspects of health status [28]. Improvements continued to be observed at 15-month follow-up, although the authors found no additive benefit for a combined pharmacological–cognitive–behavioral approach. Slaughter et al. tested sertraline in an open-label trial for the treatment of major depression in persons with RA and found it to be an effective treatment option [29].

Self-management
Warsi et al. found that participation in self-management programs resulted in significant improvements in pain and disability for persons with RA [30]. Programs that seek to reduce pain, stress, and depression have been the primary focus in the literature on self-management in RA [31,32]. Indeed, the US National Arthritis Action Plan has recommended that self-management programs be incorporated into standard rheumatological care. Most importantly, self-management programs have been shown to result in long-term benefits, including the potential offset of medical costs [33].

In general, management of pain is a primary concern for persons with RA [2]. Cognitive–behavioral programs for pain management typically incorporate treatment modalities such as relaxation training, strategies for improving cognitive coping mechanisms, communication training, assertioniveness training, strategies for improving problem-solving skills, and education for family members in behavior modification [34]. In their review of the literature, Parker et al. found the preponderance of evidence to support the utility of cognitive–behavioral interventions that address pain management and the value of including such interventions in standard rheumatological care [34].

Parker et al. designed a randomized controlled trial that examined the efficacy of a cognitive–behavioral self-management program for chronic pain in RA [2]. Participants in the treatment group were exposed to an intensive pain management intervention that included problem-solving techniques, relaxation training, strategies for attention diversion, and training in family dynamics and communication. Overall, participants in the treatment group demonstrated significant improvement in coping strategies and increased confidence in their ability to manage pain; benefits were maintained at 12-month follow-up. Those participants who underwent the cognitive–behavioral intervention and had the highest program adherence reported fewer feelings of helplessness and demonstrated the most significant improvement in their ability to cope with pain. O’Leary et al. also conducted a randomized controlled trial examining the effects of a cognitive–behavioral program designed to improve perceived self-efficacy for managing pain, and the authors reported improvements in perceived self-efficacy, pain, joint inflammation, and psychosocial functioning [35]. Intra-group analyses showed that persons with RA who participated in the program also coped better, experienced less depression or stress, and displayed improvements in sleep.

Conclusion
Several themes are apparent in the literature on psychological factors in RA. First, a sizable percentage of persons experience emotional distress during the course of RA. In general, RA requires extensive psychological adaptation to the challenging symptoms and losses in functional status. Depression, in particular, is more prevalent in persons with rheumatic diseases such as RA than in those without serious chronic conditions [20]. Depression in RA has been found to be associated with negative health consequences, impaired functional status, and higher usage of health services, although the evidence in support of the relationship between depression and higher usage of health services is less strong [36].

Secondly, chronic pain in RA can be influenced by psychological variables such as perception and coping. Specifically, coping styles such as pain catastrophizing, pain-related anxiety or fear, and helplessness have been found to be associated with higher pain levels [15]. Conversely, persons who experience days of greater coping efficacy have a greater tendency to use relaxation exercises, make cognitive attempts at re-defining pain, and seek spiritual support [16].

Finally, the preponderance of evidence supports the influence of psychological variables on functional status in RA and justifies a comprehensive biopsychosocial framework for symptom management. Research on adjunctive treatment options for management of psychological issues in RA has been generally encouraging, and outcome studies have demonstrated the efficacy of both psychopharmacological and self-management interventions for persons with RA.
Disclosure
The authors have no relevant financial interests to disclose.

References

INTERNATIONAL JOURNAL OF ADVANCES IN RHEUMATOLOGY Vol 5 No 2 2007 43
Crohn’s disease (CD) and ulcerative colitis (UC) are chronic forms of inflammatory bowel disease (IBD) that can cause lifelong morbidity. Symptoms typically start at the age of 20–30 years [1]. CD is a transmural inflammation that may involve any part of the alimentary tract but mainly affects the ileocolonic area and the perianal region (Fig. 1). UC is a more superficial inflammation, affecting only the colon (Fig. 2). This gut inflammation may lead to symptoms of abdominal pain, diarrhea (sometimes bloody), weight loss, and fever. In about one-third of patients, extraintestinal manifestations can be present, affecting the joints, eyes, skin, or liver [2]. Articular involvement may include peripheral arthritis and axial involvement, conditions which belong to the spondyloarthropathy (SpA) family. Peripheral arthritis preferentially affects the joints of the upper or lower limbs in an asymmetrical pattern. The prognosis is generally good, with spontaneous resolution being the norm, and progression to a chronic and erosive state occurring in only a minority of patients [3]. Unfortunately, the prognosis for axial involvement is less favorable.

Spinal inflammation starts with inflammatory back pain, is insidious in character, improves with exercise, and is associated with morning stiffness. Radiological examination can reveal the presence of sacroiliitis (possibly associated with spondylitis), which is characterized by squaring, erosions, syndesmophytes, zygapophyseal joint involvement, discitis, and ankylosis.

Exact prevalences of articular involvement vary across studies according to the criteria applied. Clinical symptoms of peripheral arthritis may be observed in 10–20% of patients, but radiological evidence of sacroiliitis, whether associated with inflammatory back pain or not, has been reported in approximately 20–25% of cases in several studies [4–6]. With the use of more sensitive detection methods, such as computed tomography and magnetic resonance imaging (particularly the latter), even higher prevalences have been reported [7].

A diagnosis of ankylosing spondylitis (AS) based on the modified New York criteria [8], which include clinical components (lower back pain and morning stiffness for >3 months associated with decreased mobility of the lumbar spine and limited chest expansion) and radiological components (grade 2 bilateral or grade 3–4 unilateral sacroiliitis), is reported in only 7–10% of patients [4,5]. In contrast to idiopathic AS, which is almost always associated with human leukocyte antigen B27 (HLA-B27), the association with this antigen is much less pronounced in IBD-related AS, occurring in 25–75% of cases [4–6].

Enthesitis, which is an inflammation of the muscular or tendinous attachment to the bone, is present in approximately 10% of patients with CD [4,9]. The most frequently involved peripheral entheses are:

- The insertion of the plantar fascia at the calcaneum.
- The insertion of the Achilles’ tendon at the posterior surface of the calcaneum (Fig. 3).
- The insertion of the patellar ligament at the tibial tuberosity.

Address for correspondence: Martine De Vos, Department of Gastroenterology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium. Email: martine.devos@ugent.be
Evidence for similar gut–joint enteropathy in SpA and CD

Not only is there a similar arthropathy observed in SpA and CD, but gut inflammation in these diseases also has overlap. In 60% of patients with SpA who have no clinical evidence of CD, microscopic inflammation has been found in the terminal ileum and colon [10–13]. Two types of inflammation have been described: acute inflammation, as seen in infectious colitis; and a more chronic inflammation resembling CD [14].

In a study of patients with the latter type, an evolution to overt CD was observed in 13% of cases, supporting the concept of preclinical CD in such patients. In addition to this overlap, a striking parallel exists between the activity of inflammation in the joint and the intestine [15].

In recent years, gut–joint enteropathy has been studied in detail in intestinal and synovial biopsy samples. The adhesion molecule αEβ7 is involved in the interaction between lymphocytes and epithelial cells, and its expression on interleukin-2 (IL-2)-expanded T cell lines derived from intestinal mucosa has been observed to increase similarly among patients with CD and those with AS, with or without gut inflammation [16]. In addition, E-cadherin (a ligand of this adhesion molecule) has also been reported to be upregulated in these disorders [17]. The immune infiltrate in the gut mucosa observed in patients with SpA, even in the absence of inflammation, suggests the presence of early intestinal alterations. Increases in the numbers of follicles in the ileum and colon, CD11c-expressing leukocytes in the ileum, CD11a- and vascular cell adhesion molecule-1-expressing cells in the colon, and CD68+ macrophages suggest that there is augmented antigen handling and presentation and more frequent maturation of naïve T cells to memory T cells in the gut of patients with SpA [18].

Inflammatory synovial lesions in SpA are characterized by the manifestation of a lymphocytic infiltrate. The differential expression of β7 integrins on T cells in the synovium of patients with SpA suggests that there is differential infiltration by intestinal lymphocytes [19]. Binding of gut-derived leukocytes to synovial vessels has been demonstrated and is probably linked to the presence of cognate antigens at both sites. This binding can be inhibited by the blockade of vascular adhesion protein-1 [20]. This observation supports the role of gut-derived immune cells in SpA joint inflammation.

The selective increase in the level of CD163+ macrophages in the synovium and intestine of patients with CD or SpA suggests an additional role for this subset of macrophages. In a synovial study, CD68+ macrophages were found at equal levels in SpA and rheumatoid arthritis (RA); however, the number of MRP8+ cells (infiltrating macrophages) was lower in cases of SpA than in cases of RA, while CD163+ cells (resident macrophages) were more prominent in the synovial lining and sub-lining layer in the former [21]. A relationship has been found between global disease activity and the presence of inflammatory infiltrate with CD163+ cells and polymorphonuclear (PMN) cells [22,23]. Although sacroiliac joints are difficult to examine, preliminary studies of sacroiliac biopsies in patients with SpA and early and active sacroiliitis have demonstrated an infiltration of T cells and macrophages, suggesting a similar mechanism [24]. Finally, raised serum levels of anti-*Saccharomyces cerevisiae* antibodies have been reported in patients with AS or undifferentiated SpA, thus reinforcing the link with CD [25].

Evidence for genetic predisposition

The most convincing evidence for a genetic contribution to gut–joint enteropathy comes from HLA-B27-transgenic rats. These animals develop an illness similar to SpA that involves arthritis, enthesitis, skin and nail lesions, and ocular and intestinal inflammation [26]. Furthermore, the severity of the clinical disease is correlated with the number of copies of HLA-B27 expressed in the transgenic animal [27].

The role of HLA-B27 in the development of extraintestinal manifestations of IBD is less clear. Among European Caucasian people, the prevalence of HLA-B27 positivity is approximately
4–13% in the general population, 50% in patients with enteric infection-related reactive arthritis, and 90% in patients with idiopathic AS. In the case of enteric infection-related reactive arthritis, HLA-B27 does not appear to predispose individuals to the infection itself, but it does increase the risk of more severe and prolonged arthritis [28].

In patients with peripheral arthritis associated with psoriasis or IBD, the prevalence of HLA-B27 positivity is equal to that in the general population. In contrast, the prevalence increases to 50–70% in patients with sacroiliitis and spondylitis, but this is still considerably lower than the 90% observed in idiopathic AS [5]. One study of CD demonstrated an increase in HLA-B27 positivity from 14% in patients who had pain associated with sacroiliitis to 78% in patients who fulfilled the criteria for AS [29]. This suggests that sacroiliitis in CD is usually not associated with HLA-B27 per se, but is likely to develop into AS in HLA-B27-positive patients. Similarly, HLA-B27 positivity in patients with SpA is related neither to associated gut inflammation nor to development into CD [10]. Chronic inflammation is more frequent in HLA-B27-negative patients than in HLA-B27-positive patients (58% and 37%, respectively), suggesting that other genetic factors play a role [10].

Following the identification of a linkage region on chromosome 16 in CD and in AS, several additional studies have excluded CARD15 polymorphisms associated with CD as putative susceptibility variants for SpA or AS in general [30–34]. However, in a more recent study, a strong relationship was found in patients with SpA between the development of chronic gut inflammation and the carriage of R702W, G908R, or 1007fs variants of CARD15, identifying a phenotypical subgroup more prone to develop CD [35]. A single-center study including 102 patients with CD found an association between these polymorphisms and the development of sacroiliitis [5].

Recently, a global gene expression analysis in non-inflamed colon tissue revealed 95 genes that were differentially expressed in patients with CD and patients with SpA and a history of chronic gut inflammation [36]. The use of non-inflamed samples from patients with CD offers the possibility of identifying early markers for CD, which would permit prediction of the development of CD in patients with SpA. A further focus on genes located within an arbitrary region of 5 centimorgans from a marker that showed the highest linkage to CD in at least two independent studies led to the selection of 18 candidate genes. One of the candidates led to the identification of a possible new disease-modifying gene, MTF1, located at 1p33 (near locus IBD7) [37].

**Evidence for altered innate immunity**

Reactive arthritis seems to result from a T cell-mediated immune response to bacterial antigens and degradation products circulating from the gut to the joints. The list of pathogens associated with reactive arthritis is small; the most frequent initiators are:

- *Shigella flexneri.*
- *Salmonella typhimurium.*
- *Yersinia enterocolitica.*
- *Campylobacter jejuni.*
- *Chlamydia trachomatis.*

Apart from *C. trachomatis*, all of these are intracellular, aerobic (obligate or facultative), invasive, Gram-negative bacteria with a lipopolysaccharide (LPS)-containing outer membrane. The presence of pathogenic bacterial antigens and LPS has been demonstrated in the synovium, as has the response of synovial fluid T cell clones to the antigens [38–40]. The reverse transcriptase polymerase chain reaction has been used to demonstrate the presence of bacterial RNA in joint tissue, providing direct evidence of bacterial infection [41]. Viable microbes had not previously been found in joint tissue from patients with SpA.

The role of HLA-B27 in this process can be deduced from data obtained from HLA-B27-transgenic rat models and other experimental observations [26,42]:

- Aberrant antigen presentation results either from the presence of specific arthritogenic bacterial peptides and the consequent circulation of activated cytotoxic T lymphocytes, or by shared antigenic recognition of B27-bound peptides between bacterial peptides and self-peptides (molecular mimicry).
- There is impaired clearance of intracellular bacteria by HLA-B27 with persistent traffic of dendritic cells and sharing of homing receptors between the synovium and gut, resulting in increased cell adhesion and transmigration.
- The most distinguishing characteristic of HLA-B27 is the binding groove, which interacts with the side chain of the second amino acid residue of the bound peptide. Misfolding of HLA-B27 can occur during the intracellular assembly process, leading to activation of nuclear factor-κB (NF-κB) and secretion of proinflammatory cytokines, and the formation of heavy chain homodimers with potential immunogenic capacity.
- The frequent association between arthritis and flare-ups of IBD, and the transitory character of the inflammation, link the arthritis to an invasion of bacteria through a disrupted bowel wall [43,44]. Axial involvement evolves independently of gut inflammation and is possibly related to a more profound and longstanding alteration in the innate immune response to intestinal flora.
Innate immune cells of potential importance are CD163+ macrophages. Typical features of synovitis in SpA are the increased levels of CD163+ resident tissue macrophages and PMN cells [23]. Levels of this CD163+ macrophage subset are also increased in the colonic mucosa of patients with CD, as well as in patients with SpA, irrespective of the presence of inflammation. Analysis of the link between synovial histopathology and global disease activity has indicated that disease activity is related to CD163+ resident tissue macrophages and PMN cells but not CD3+ or CD20+ lymphocytes [22]. CD163 is a cell-surface glycoprotein of the cysteine-rich scavenger receptor family group B. Functional studies of CD163+ macrophages have demonstrated their ability to produce high levels of soluble CD163 locally in joints. This soluble CD163 downregulates the activation of synovial T lymphocytes, which provides a mechanism of impaired T-cell function. Additionally, functional analysis in vitro has shown that these macrophages produce tumor necrosis factor-α (TNF-α) but not IL-10 after LPS stimulation [23]. This is surprising since stimulation with the natural CD163 ligand (haptoglobin–hemoglobin complexes) usually leads to an anti-inflammatory response of these cells, suggesting that other receptor–ligand pairs are involved in the response. An increased expression of Toll-like receptor 4 (TLR4), but not TLR2, on peripheral blood monocytes was demonstrated in patients with SpA relative to healthy controls [45]. Although an increased expression was noticed on all monocyte subsets, a significantly higher expression was found on CD163+ phagocytes, supporting the hypothesis that alterations in the TLR pathway are involved in an abnormal activation of the innate immunity-mediated inflammation seen in SpA.

Additional evidence for the role of innate immunity comes from the link between CARD15 polymorphisms and the presence of chronic gut inflammation in CD as well as in SpA [35]. CARD15 encodes an intracellular protein that binds bacterial LPS and other bacterial components and that activates the NF-κB pathway. A disturbed immunological response of host cells towards bacterial antigens has been associated with CD-related CARD15 polymorphisms. A combination of a reduced mucosal expression of α-defensins and a reduced expression of IL-1β and IL-6, leading to defective neutrophil recruitment and infiltration, may facilitate a subsequent mucosal influx of intestinal bacteria and lead to a secondary inflammatory response [46,47]. Additional genetic or local factors may contribute to the circulation of cells and bacterial antigens to extraintestinal sites.

Central role of TNF-α in CD and SpA
Growing evidence that suggests an immunological relationship between gut inflammation in SpA and CD has therapeutic consequences. Drugs used for the treatment of CD have variable effects on articular disease. Sulfasalazine has been demonstrated to be effective, especially in the treatment of peripheral arthritis [48,49]. Aminosalicylates, such as mesalamine, may have similar efficacy, although data are scarce. The use of corticosteroids is very effective in the local treatment of peripheral arthritis and enthesopathy [50]. Methotrexate has never been adequately studied in controlled trials, but the general impression is that this drug is not effective in SpA [51]. NSAIDs are the mainstay of medical therapy in SpA, but they may have deleterious effects on IBD. A recent large study including 629 outpatients with IBD demonstrated that low-dose NSAID was generally well tolerated, but that long-term and high-dose use, as is often required in treating axial symptoms, was still problematic [52].

The major breakthrough in this area was the discovery of the dramatic efficacy of TNF-α blockade in SpA, with clinical effects similar to those observed in CD [53–55]. Many studies have been published on the use of TNF-α-blocking agents in SpA [56–71]. The majority of these included patients with AS or undifferentiated SpA, but some more recent studies included patients with psoriatic arthritis [72–76]. Trials that have focused on the effect of TNF-α antagonism on SpA associated with IBD have been small and open [77–80].

In all of the studies with adalimumab and infliximab, a dramatic improvement was demonstrated in intestinal and articular variables (both clinical and laboratory-based). In AS and PsA, improvements were noted in both axial and peripheral symptoms, as well as in enthesitis. As in CD, the clinical effect of treatment was rapid and sustained if administered on a regular basis. However, an important and unexplained difference has been observed between AS and CD in terms of the efficacy of etanercept – no clear effect was demonstrated in CD, whereas the drug demonstrated similar efficacy to the other anti-TNF-α therapies in AS [81,82].

Additional evidence for the central role of TNF-α comes from mice lacking adenosine–uridine (AU)-rich elements, which develop arthritis and ileitis as a consequence of increased TNF mRNA stability [83]. Homozygous mice develop severe disease shortly after birth and survive only briefly. Heterozygous mice develop a clinical syndrome resembling CD and associated SpA 4–5 weeks after birth. TNF receptor I seems to play a dominant role in the development of arthritis as well as ileitis, whereas TNF receptor II plays a suppressive role in the development of arthritis without any effect on intestinal inflammation [83].

Other new agents studied in CD merit more focus, such as IL-10, recombinant IL-11, intercellular adhesion molecule-1 antisense oligodeoxynucleotide, and anti-α4β7. Anti-α4β7 seemed particularly promising because a selective enrichment of lymphocytes was demonstrated in synovial
infiltrates of patients with arthritis, supporting an intestinal origin. However, publication of several cases of lethal progressive multifocal leukoencephalopathy associated with reactivation of human polyoma virus led to the suspension of further commercialization of the drug.

Conclusion

TNF-α plays a role in joint and gut inflammation in SpA and Crohn’s disease, and TNF-α blockade has proven to be an extremely efficacious therapy, usually causing rapid improvement of all clinical parameters. Genetic predisposition to gut and joint inflammation seems to be partially mediated by CARD15, since mutations in this gene predispose patients with SpA and CD to gut inflammation and patients with CD to AS. In contrast, HLA-B27 seems to play only a minor role in this interaction. Further elucidation of gut–joint enteroarthritis is necessary for a better understanding of this relationship and for the development of new treatment approaches.

Disclosure

The author has no relevant financial interests to disclose.

References


Mr C, a 25 year old right-handed security officer presented to his general practitioner with a 2-week history of lethargy, loss of appetite, and night sweats. He was receiving fluoxetine for a 3-year history of depression and reported being “very stressed” following the recent birth of his first child. He had had a tattoo on his left arm 4 months previously, smoked approximately 10 cigarettes per day, and occasionally drank alcohol. The results of initial routine investigations were normal.

One week later, he was admitted to the local hospital (Pindersfield General Hospital, Wakefield, UK) with self-limiting hematemesis and shortness of breath. Aside from a body temperature of 38.6°C, clinical assessment, routine blood tests, chest X-ray, and upper gastrointestinal endoscopy revealed unremarkable results. Mr C was discharged, but 4 days later he noticed pain in his right shoulder after having a fall in a restaurant. He was referred for admission after repeat investigations revealed a white blood cell count of $18.9 \times 10^9/L$ (lymphocyte count $12.5 \times 10^9/L$, with occasional blast and plasma cells).

On admission, Mr C complained of right shoulder pain, but clinical assessment was documented to be unremarkable. The C-reactive protein level was raised (at 46 mg/L), and lymphocytosis was observed, including the presence of large reactive lymphocytes. Radiographs of the shoulder were normal and ultrasound examination of the abdomen revealed mild hepatosplenomegaly with minimal ascites. Infectious mononucleosis screening results were negative. A hematological consultation suggested probable viral illness.

Pain control was difficult, with the patient’s medication escalating from co-codamol to tramadol 100 mg three times daily with morphine supplements. By the third day, Mr C complained of severe pain in both shoulders, which was worse on the right side, and movements were documented to be painful and restricted. Sensation, reflexes, and neck movements were normal. The white blood cell count had increased to $24.5 \times 10^9/L$ (lymphocyte count $18.50 \times 10^9/L$), and serum alanine transaminase and alkaline phosphatase levels were elevated (at 99 IU/L [normal range 5–56 IU/L] and 230 IU/L [normal range 30–130 IU/L], respectively). Creatine kinase, bilirubin, and clotting profiles were normal. Since the shoulder pain was refractory to standard analgesics and required opiates, a rheumatological opinion was requested.

**Rheumatological referral**

The rheumatology team evaluated the patient and a further detailed history revealed that the shoulder pain radiated to the scapula and as far down the arm as the elbow. He also complained of fatigue, but no extra-articular symptoms were noted. Examination revealed wasting of the left supraspinatus, in addition to wasting of the infraspinatus on both sides, more prominently the left (Fig. 1). The right supraspinatus was tender with no sensory impairment. Active movements of both shoulders were painful and restricted. Passive abduction was painful and restricted to 75°, with weakness of external rotation observed bilaterally. Reflexes were normal and there was no limitation of neck movement.

Serum alanine transaminase levels had increased further to 110 IU/L, limiting the analgesia dosage. An isolated elevation of creatine kinase levels to 542 IU/L was noted. On day 5 of admission, Mr C complained of persistent pain in both shoulders and stated that he wanted to “fly out of the window.” Topical capsaicin 0.025% was added to his treatment and the ward team requested a psychiatric referral.

Viral serological studies revealed the presence of immunoglobulin G (IgG) and IgM antibodies against cytomegalovirus (CMV). By day 12 of admission, the pain had subsided, but muscle wasting and weakness appeared more pronounced.
Two weeks later, there was resolution of all abnormal hematological and biochemical parameters. The patient was discharged and given oral analgesics, with a follow-up appointment scheduled at the rheumatology outpatient clinic at Pontefract General Infirmary (Pontefract, UK) after 1 week.

Post-discharge
At the rheumatology outpatient visit, Mr C complained of numbness over the right lateral upper arm and radial aspect of the forearm, and weakness of the right serratus anterior was noted with winging of the scapula (Fig. 2). Nerve conduction study (NCS) and electromyogram (EMG) results were compatible with neuralgic amyotrophy. The infrequent association of this condition with HIV was discussed with the patient, and he agreed to attend the local genito-urinary service for testing; results were negative. Mr C and his partner were counseled about the likely course of neuralgic amyotrophy, and the patient continued with physiotherapy. Nine months later, there is a slight improvement in muscle power, although wasting largely persists. The patient’s description of his experiences is provided in the box above.

The patient’s view.
In the summer of 2005, I was in a restaurant when I passed out. I was taken to hospital for an examination and then released the same day. Two days later, I received a phone call from my GP [general practitioner] with news that my white blood cell level was unusually high, and I was asked if I would go to hospital again.

While in the hospital, I began feeling a lot of pain down the back of my neck, across both shoulders and my arms, mainly the right one. I was given a variety of painkillers and underwent a number of tests. At first, I was told that I might have leukemia, but the test results for that were negative. Next it was said that I could be HIV positive; I went for testing for that as well, but the results also came back negative.

The pain I endured was intolerable most of the time, and no amount of analgesia seemed to work. I was in the hospital for >3 weeks; it was somewhat scary because nobody knew what was wrong with me. I lost a lot of muscle across my back and right arm, which meant that I could not use my right arm and for 2 months could not even hold a pen. Following discharge, I was sent to another hospital to have more tests done; the results suggested that I was suffering from a condition known as neuralgic amyotrophy.

Most medical professionals who I have encountered have not heard of neuralgic amyotrophy; for instance, neither my GP nor my physiotherapist was aware of it. I have had many visits for physiotherapy and the use of my arm has undergone a long, slow, and painful recovery, but it is still nowhere near its normal state after more than a year. I experience many different sensations across the “infected area,” some muscle twitching and spasms, numbness in my forearm, and reduced lifting strength. I can now lift 10 kg but find doing so very strenuous and uncomfortable.

The condition has also had a psychological impact on me. I used to be in the armed forces and then worked in security, which meant that I was reasonably fit, strong, and active. Since developing the condition, I have been feeling depressed because I can do few of the things I used to. For a long time, I could not shave or bathe myself properly, and I also needed help to get dressed. In addition, my partner and I have a young daughter. I could not hold her in my arms, change nappies [diapers], or play with her as other parents could, which was very upsetting.

At present, I am still working with physiotherapists and a specialist, but it is an extremely slow recovery process. Some days are good; some are not.
Discussion

Approximately two-thirds of cases of neuralgic amyotrophy (also known as Parsonage–Turner syndrome [1]) are unilateral, with the right arm being affected more frequently. It presents with rapid onset of excruciating pain in or around the shoulder that may radiate down the arm and up to the neck. Shoulder movements are painful and restricted, with prominent muscle wasting observed in more than three-quarters of patients. The pain typically subsides as paresis of the muscles innervated by the brachial plexus develops, usually within a time period between a few hours and 3 weeks. Muscle involvement is usually patchy around the shoulder; the diaphragm and cranial nerves are occasionally affected. Sensory symptoms with corresponding deficits may be noted, and tendon reflexes may be either normal or diminished.

An immune-mediated inflammatory reaction against brachial plexus nerves has been postulated as a probable mechanism [2]. Possible triggers include viral illness (e.g. Epstein–Barr virus and parvovirus), surgery, immunization, and childbirth. CMV has rarely been implicated [3]. Diagnosis is clinical in nature and investigations help to exclude other conditions. NCS and EMG results demonstrate axonal degeneration with patchy denervation, which is usually bilateral, even in a clinically unilateral syndrome. Management is with adequate analgesia (although this may not work), and supportive treatment including physiotherapy and counseling. The role of corticosteroids is unclear, but these agents may reduce the pain and severity. Recovery is slow, but the overall prognosis is good, with recovery reported in 36%, 75%, and 89% of cases by the end of the first, second and third year, respectively; the recurrence rate observed is approximately 5% [4].

Case Study Editor’s comments

The authors present a very unusual case of shoulder pain and dysfunction that highlights the importance of musculoskeletal manifestations of systemic illness. Of note in this case were the severity of pain and the paucity of clinical signs early in the disease course. This is often a difficult scenario for the clinician, especially in the shoulder, where referred pain is relatively common. As with many clinical scenarios, further observation and passage of time revealed more specific signs and enabled a diagnosis to be made. In neuralgic amyotrophy, weakness tends to occur approximately 2 weeks after the onset of pain. In young patients, consideration should be given to a distinct hereditary form that has been localized to the gene coding for septin 9 (SEPT9), which is located on chromosome 17q. This affects males and females equally and is inherited in an autosomal dominant fashion. It is characterized by recurrent attacks that are frequently bilateral. There may also be dysmorphic facial features such as facial asymmetry, hypotelorism, and a long nasal bridge. The cause of Mr C’s condition would appear to be CMV infection, but trauma not involving the shoulder may also be implicated. As with many scenarios in medicine, cause and effect is nearly impossible to demonstrate.

Disclosure

The authors have no relevant financial interest to declare.

References

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

**PATHOGENESIS**

**FcγRIIb controls bone marrow plasma cell persistence and apoptosis**


Failure to control the lifespan of autoreactive plasma cells will lead to continuous production of autoantibodies, which are the hallmark of autoimmune diseases. It has been shown that cross-linking of a receptor for the constant part of immunoglobulin G – “fragment crystallizable” γ receptor Iib (FcγRIIb) – induces apoptosis. Therefore, it was hypothesized that a lack of expression of FcγRIIb leads to autoantibody production. Indeed, mice prone to developing systemic lupus erythematosus lacked FcγRIIb expression on their plasma cells. These findings are important because it is the first time that it has been shown that FcγRIIb controls bone marrow plasma cell persistence and that defects contribute to autoantibody production.

Most serum immunoglobulin G is made by plasma cells in the bone marrow. These long-lived plasma cells can survive in an anatomical “niche” in which essential growth factors prevent them from dying. These survival niches limit the plasma cell capacity of the bone marrow by their physical space.

The study authors showed that immunization reduces the previously generated plasma cell numbers, but that this reduction was dependent on expression of “fragment crystallizable” γ receptor Iib (FcγRIIb), most probably through the existence of immune complexes that bind to FcγRIIb, inducing plasma cell apoptosis. Plasma cells with higher levels of FcγRIIb expression were more susceptible to apoptosis.

These findings suggest that immune complexes promote apoptosis and subsequently control plasma cell numbers both in the bone marrow and in inflammatory lesions. Failure of plasma cell apoptosis when the level of FcγRIIb expression is low results in autoantibody production and the formation of more immune complexes; therefore, a vicious cycle results that drives pathological inflammation.

Address for reprints: K Smith, University of Cambridge School of Clinical Medicine, Addenbrooke’s Hospital, Cambridge, CB2 2OY, UK. Email: kgc2@cam.ac.uk

**Tenosynovitis and osteoclast formation as the initial preclinical changes in a murine model of inflammatory arthritis**


Ample data from clinical intervention studies exist to show that early initiation of therapy is beneficial in inflammatory arthritis. In a model of tumor necrosis factor-transgenic mice that develop a rheumatoid arthritis-like systemic and destructive arthritis, structural damage was found to begin before the onset of clinical symptoms of arthritis and involve tendon sheaths as well as adjacent cartilage and bone. These findings highlight the importance of tenosynovitis as an initiating feature of arthritis and underscore the relevance of early initiation of effective therapy.

In transgenic mice that overexpress human tumor necrosis factor, the preclinical stage of joint inflammation can be studied before the appearance of any clinical symptoms of swelling.

In this study, anatomical sections from transgenic mice were examined, and it was found that the initial pathological change was tendon effusion rather than synovitis. Shortly thereafter, massive infiltration of inflammatory cells led to hyperplasia of the synovial lining. Inflammatory pannus formation was further increased by an influx of granulocytes and macrophages. Over time, there was an increase in interleukin-1 and interleukin-6 levels. In order to determine the onset of bone erosions, the presence of osteoclasts was monitored: these cells were found to be present in preclinical
Effects of short-term infliximab therapy on autoantibodies in systemic lupus erythematosus


This series of experiments demonstrated that autoantibody formation is common in patients with systemic lupus erythematosus who are treated with a tumor necrosis factor-α antagonist and may be due, in part, to a corresponding increase in the level of apoptosis.

The authors of this article have previously reported on an open-label study of the treatment of seven patients with systemic lupus erythematosus who received a short course of infliximab [1]. Clinically, this treatment was associated with a prolonged reduction in the level of proteinuria, a transient improvement in synovitis that returned quickly after treatment was stopped, and an absence of disease flares. In the current article, the authors provide a detailed analysis of the autoantibody levels of the patients included in this study.

Antibodies to double-stranded DNA (dsDNA) were present in six of the seven patients before infliximab treatment, and antibodies levels increased in five of these patients, peaking about 4 weeks after the fourth and final dose of infliximab. dsDNA antibodies did not develop in the single patient without them at the start of treatment. Elevated levels returned to normal after the course of therapy, but they increased again in two patients who were retreated with infliximab. Additionally, the levels of antibodies to chromatin and histone increased in six patients and four patients, respectively. Finally, immunoglobulin M anticardiolipin antibodies developed in four of the seven patients.

In the same article, the authors describe a series of in vitro experiments in which peripheral blood mononuclear cells incubated with tumor necrosis factor-α (TNF-α) demonstrated an increase in apoptosis upon withdrawal of TNF-α (such as might occur in vivo after administration of a TNF-α antagonist).

The authors conclude that treatment with a TNF-α antagonist can commonly result in increased levels of antibodies directed at self-antigens. In addition, they propose a potential mechanism: the increased availability of self-antigens following an increase in the level of apoptosis.


Address for reprints: M Aringer, Department of Rheumatology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Email: martin.aringer@meduniwien.ac.at

Rituximab treatment in patients with IVIg-dependent immune polyneuropathy: a prospective pilot trial


Intravenous immunoglobulin (IVIg) is an established therapy for patients with chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy. In a small study in six patients who had been treated with IVIg for an average of 5 years, it was found that four infusions of rituximab 375 mg/m² at weekly intervals resulted in a reduced need for IVIg in two patients, no change in one patient, and an increased need in three patients.

Depletion of B cells by rituximab (anti-CD20 antigen) is beneficial in immune-mediated neuropathies where intravenous immunoglobulin (IVIg) is used. It has been suggested that these disorders are associated with antibody-mediated attacks on the nervous system.

The investigators sought to determine the effect of rituximab 375 mg/m² once weekly for 4 weeks in six patients who had been treated with IVIg for an average of 5 years. Two of the patients had chronic inflammatory demyelinating polyneuropathy, two had multifocal motor neuropathy (MMN), one had neuropathy associated with Sjögren syndrome, and one had neuropathy associated with anti-myelin-associated glycoprotein antibodies. The study’s primary endpoint was a reduction in the cumulative IVIg dosage of ≥25% 1 year after rituximab therapy, compared with the previous year.

Rituximab resulted in clinical benefit in only two of six patients (one with Sjögren syndrome and one with MMN); there was no change in the need for IVIg in one patient and an increase in three patients. No major side effects were seen in any of the patients. Larger studies are necessary to test whether subpopulations exist among this patient group in which rituximab may be used as an IVIg-sparing drug.

Address for reprints: K Gorson, Department of Neurology, Caritas St Elizabeth’s Medical Center, Tufts University School of Medicine, 736 Cambridge Street, Boston, MA 02135, USA. Email: kengorson@comcast.net
Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study


In this analysis of data from a large registry of patients treated with tumor necrosis factor-α (TNF-α) antagonists, it appeared that treatment with a second agent after discontinuing the first was largely successful. In cases of failure, the reason (inefficacy or the occurrence of an adverse event) was more likely than not to be the same as for the first treatment failure.

As the number of patients being treated with tumor necrosis factor-α (TNF-α) antagonists has grown worldwide, the number of patients with an inadequate response to therapy has also increased. Clinical trials of the newer biological agents abatacept and rituximab have demonstrated their benefit in this population. Another option is to substitute one TNF-α antagonist for another, but data for this have only previously been available from small case series.

In this article, the authors report on the British Society for Rheumatology Biologics Register experience with switching from one agent to another. At the time of this data acquisition, they had recorded information on 6739 treatment starts on the three available agents, adalimumab, etanercept, and infliximab. During a mean follow-up of 15 months, 65% of these patients remained on their initial therapy. Of those who discontinued the first agent, 12% did so because of inefficacy and 15% did so because of the occurrence of an adverse event (AE). Many of these patients (primarily from the former group) went on to start treatment with a second TNF-α antagonist.

After additional follow-up for a mean of 6 months, 27% had again stopped treatment with the second agent, about half owing to inefficacy and half owing to an AE. When the survival curves for remaining on therapy were analyzed and adjusted for potentially confounding variables, it appeared that in patients discontinuing their second course of therapy, the reason was related to that for the discontinuation of the first treatment course. Those stopping their first drug owing to inefficacy had an approximately three-fold increased risk of stopping the second drug for the same reason; likewise, those stopping their first therapy because of an AE had a two-fold increased risk of developing a treatment-halting AE during the second course of therapy.

While this study did not specifically examine the clinical response to the second treatment course, the implication of the survival analysis is that most patients had a response to a second treatment that was sufficient to continue the therapy.

Address for reprints: D Symmons, Arthritis Research Campaign Epidemiology Unit, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, UK. Email: deborah.symmons@manchester.ac.uk

Treatment with rituximab affects both the cellular and the humoral arm of the immune system in patients with SLE


In this prospective study, the effects of rituximab treatment on immunological parameters – such as the presence of autoantibodies and the frequency of circulating B and T cell subsets – were evaluated in patients with systemic lupus erythematosus.

Evidence suggests that B cells play a role in the pathogenesis of systemic lupus erythematosus (SLE), since not only do quantitative and functional B cell abnormalities occur in patients with SLE, but B cells also produce autoantibodies against a series of nuclear antigens and give rise to immune complex formation involved in tissue damage. Recent studies on patients with SLE showed that treatment with rituximab – an antibody targeting CD20, which is solely expressed on B cells (i.e. it is not expressed on pro-B cells or antibody-secreting plasma cells) – is safe and improves several disease manifestations. Analysis of rituximab’s effects on different components of the immune system, as undertaken in this study, provides an opportunity to dissect the actual role of B cells in the pathogenesis of SLE.

Eleven patients with active SLE who did not derive an adequate response from conventional therapy, including cyclophosphamide, received four weekly infusions of rituximab (375 mg/m²) and were followed for up to 30 months after rituximab therapy. Rituximab therapy was accompanied by cyclophosphamide (0.5 g/m²) for the first and fourth infusion and by corticosteroids throughout treatment. The levels of certain B and T cell subsets, serum autoantibodies, and immunoglobulin (Ig) types were measured before and at several time points after rituximab administration.

Notably, all patients showed clinical improvement after rituximab treatment, as reflected by a decreased Systemic Lupus Activity Measure index score. The level of circulating B cells was reduced after rituximab treatment in all patients. A significant correlation was found between the pretreatment frequency of B cells and the time until return to the circulation: individuals with more pronounced B cell lymphopenia had a slower return of B cells to the circulation (p=0.015).
The small number of B cells remaining after treatment were of the memory, double-negative (IgD-CD27-), and CD5+ phenotype; they might have been more resistant to CD20 depletion or could have extravasated from the lymphoid tissues. A reduction in the levels of disease activity-associated IgG anti-double-stranded DNA and anti-C1q antibodies and total IgM and IgE was seen; however, no significant changes were seen in serum levels of total IgA, total IgG, or antibodies against Ro52, Ro60, La44, measles, or tetanus. An unexpected cellular effect was seen after rituximab administration – an increased level of activated CD4+ and CD8+ T cells and CD25brightFOXP3+ regulatory T cells.

The authors conclude that in patients with SLE, rituximab therapy not only causes changes in B cell frequency, phenotype, and effector functions, but may also affect certain T cell subsets; in concert, these effects may lead to amelioration of the disease.

Address for reprints: T Vallerskog, Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, S-171 76 Stockholm, Sweden. Email: therese.vallerskog@ki.se

### EPIDEMIOLOGY

#### Polyarticular psoriatic arthritis is more like oligoarticular psoriatic arthritis than rheumatoid arthritis


Helliwell PS, Porter G, Taylor WJ; CASPAR Study Group.

Patients with polyarticular disease and psoriasis can be classified as having seronegative rheumatoid arthritis (RA) or polyarticular psoriatic arthritis (PsA). The CASPAR (Classification of Psoriatic Arthritis) database contains characteristics of 588 patients with physician-diagnosed PsA and 525 controls with other forms of inflammatory arthritis (70% with RA). In this article, the authors report how the characteristics seen with polyarticular PsA were more like those associated with other forms of PsA than with RA, suggesting that the patients diagnosed with polyarticular PsA have been classified correctly.

Clinical distinction between patients with different forms of arthritis is necessary for treatment decisions, outcome considerations, and the study of risk factors to unravel pathogenetic mechanisms.

In this study, patients with psoriatic arthritis (PsA) were classified as having polyarthritis (which included arthritis mutilans) or non-polyarthritis (which, in addition to oligoarthritis, included distal interphalangeal predominant arthritis and cases with any spinal involvement). These two subgroups were compared with a third subgroup: patients with polyarticular rheumatoid arthritis (RA).

The three subgroups differed with regard to age, sex, total number of involved joints, disability score, and symmetry. No differences were found in autoantibody status, presence of enthesitis, and the occurrence of spinal pain and stiffness. Analysis of radiological features, revealed that syndesmophytes were found to be characteristic of PsA, particularly non-polyarthritic PsA, while distal interphalangeal erosions occurred at a similar frequency in the two PsA subgroups but were less common in the RA group.

These detailed comparisons provide further evidence for PsA being a separate disease and highlight the need for new classification criteria to be developed.

Address for reprints: PS Helliwell, Academic Unit of Musculoskeletal and Rehabilitation Medicine, University of Leeds, 36 Clarendon Road, Leeds, LS2 9NZ, UK. Email: p.helliwell@leeds.ac.uk

#### Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis

Amin S, Niu J, Guermazi M et al.


This prospective, 30-month study revealed that cigarette smoking may worsen both the progression and the symptoms of knee osteoarthritis in men, but uncertainty remains about the underlying mechanisms.

Multiple studies have suggested that cigarette smoking is associated with both the risk and severity of rheumatoid arthritis. However, little is known about the impact of smoking on osteoarthritis (OA). In this study, the authors assessed the impact of smoking on the risk of cartilage loss and pain in patients with OA.

Men participating in a prospective, 30-month study of the natural history of OA (n=159) were analyzed. Women were included in the larger study but not in this subanalysis, owing to a low reported incidence of smoking (4%). The men underwent magnetic resonance imaging for their more symptomatic knee at baseline, 15 months, and 30 months. Demographical data, including age and body mass index (BMI), were collected at baseline, and smoking history inquiries were made at baseline and 15 months. Knee pain severity was measured at all three time-points using a visual analog scale pain score (0–100 mm).

Of the cohort, 12% of men were current smokers at the baseline visit. Smokers were generally younger and leaner than the non-smokers. However, after adjusting for age, BMI, and baseline cartilage scores, smokers were at increased...
risk of cartilage loss at the medial tibiofemoral and patellofemoral joints. Smokers also had higher pain scores at baseline and follow-up. Although the mechanisms underlying this observation are uncertain, this study suggests that smoking may accelerate the progression of symptomatic knee OA in men.

Address for reprints: S Amin, Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA. Email: amin.shreyasee@mayo.edu

Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study

Evidence exists to implicate immunopathogenic mechanisms in the neuropsychiatric (NP) events seen in patients with systemic lupus erythematosus (SLE); however, the lack of specificity of the majority of NP manifestations raises the possibility that alternative etiologies may play a role. Clarification of this area of uncertainty would have major implications for the management of patients with SLE who present with NP events.

The aim of the present study was to evaluate the prevalence of NP events that are directly attributable to SLE. The study design was based on an international, multicenter inception cohort of patients with SLE. All 572 patients who were recruited fulfilled the American College of Rheumatology (ACR) classification criteria for SLE.

Study enrollment was encouraged as soon as possible after diagnosis, within a predefined enrollment window. Within the window, 158 (27.6%) of the 572 patients had one or more NP events and 54 (9.4%) had two or more events (the maximum number of events was six). A total of 242 NP events were recorded, and these covered 15 of the 19 NP syndromes. A contribution of non-SLE factors was identified for 76 (31.4%) of the 242 events. In the total cohort, 35 (6.1%) of the patients had 46 NP events that were deemed to be directly attributable to SLE. Regardless of attribution, patients with NP events had reduced quality of life and increased disease scores (based on the Short Form-36 Health Survey and the Systemic Lupus International Collaborating Clinics/ACR Damage Index) relative to patients with no NP events.

In conclusion, only a minority of NP events could be attributed to SLE itself.

Address for reprints: JG Hanly, Division of Rheumatology, Nova Scotia Rehabilitation Centre, 2nd Floor, 1341 Summer Street, Halifax, NS, B3H 4K4, Canada. Email: john.hanly@cdha.nshealth.ca

Power Doppler sonography and pulse-inversion harmonic imaging in evaluation of rheumatoid arthritis synovitis

This examination of two ultrasound techniques confirmed that ultrasonography can rapidly identify the effects of a short course of oral corticosteroids on synovial tissue vascularity.

An important tool in the management of rheumatoid arthritis (RA) is the ability to make a rapid assessment of response to therapy. Although the ultimate goal of treatment may be reduction of structural damage, early recognition of synovial changes leading to this damage, such as hypervascularity, may help to identify meaningful therapeutic response in a more timely fashion. In this study, the ability of two ultrasonographical techniques to measure the acute response to corticosteroid therapy in patients with active RA was evaluated.

Patients with RA who had a 28-item disease activity score (DAS28) of >3.2 (n=14) were identified and treated with a short course of prednisolone to reduce inflammation (50 mg/day for 3 days, followed by 25 mg/day for 4 days). Ultrasound examinations and measurements of the levels of laboratory markers of inflammation were performed at baseline and after therapy. Sonography was carried out using power Doppler to measure blood flow and a newer technique known as pulse-inversion harmonic imaging (PIHI). PIHI makes use of a microbubble contrast material that is injected intravenously and clears rapidly via the lungs. This intravascular contrast allows for better distinction between the vascular space and non-vascular tissue.

All patients experienced clinical improvements after treatment, with reductions in the numbers of swollen and tender joints, DAS28 values (mean reduction from 4.9 to 3.6), C-reactive protein levels, sedimentation rates, and rheumatoid factor titer values. When the joints with the greatest hypervascularity at baseline were selected for sonographical examination, the mean power Doppler score
was reduced after therapy, although no change was demonstrated in six of the 14 patients. By contrast, PIHI showed significant reductions in synovial blood flow in all patients.

This study demonstrates that ultrasonography, and in particular PIHI, is a potential tool for rapid assessment of synovial response to therapy in RA. While there are likely to be uses for these techniques in clinical practice, they may have greatest utility in clinical trials, where rapid assessment of the biological effects of new therapeutic compounds can help to determine which compounds are appropriate for further study.

Address for reprints: C Schueller-Weidekamm, Department of Diagnostic Radiology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Email: claudia.schuelle-weidekamm@meduniwien.ac.at

**GENETICS**

A functional polymorphism in the 5’ UTR of GDF5 is associated with susceptibility to osteoarthritis

Miyamoto Y, Mabuchi A, Shi D et al.


Osteoarthritis (OA), the most common form of arthritis in humans, has been shown by epidemiological and genetic studies to be a polygenic disease. The authors of this letter published in *Nature Genetics* report on findings that link the gene encoding growth differentiation factor 5 (GDF5) to OA susceptibility. The results suggest that a decrease in GDF5 expression is involved in the pathogenesis of OA.

The gene encoding growth differentiation factor 5 (GDF5) – a member of the transforming growth factor-β superfamily – is known to play a role in joint formation, with mutations in both mice and humans having been linked to abnormal articular development. Various findings have implicated GDF5 in the pathogenesis of osteoarthritis (OA), particularly in the hip. For instance, involvement of the hip joint has been seen in some patients with type C brachydactyly, which is a disorder linked to GDF5 mutations [1,2]. The current authors undertook genetic analysis in Japanese and Chinese populations to shed more light on the link between GDF5 and OA.

Two independent studies revealed several single nucleotide polymorphisms (SNPs) in the GDF5 region that were significantly associated with hip OA. Of these SNPs, the strongest association was found for one lying in the 5’ untranslated region of GDF5 (rs143383). The frequency of the susceptibility allele (+104T) was 83.6% among individuals with hip OA and 74.0% among controls. The odds ratio of the susceptibility allele was calculated as 1.79 (95% confidence interval [CI] 1.53–2.09). Noting that observed associations with OA can be affected by confounding factors (e.g. age, body mass index, and sex), the researchers tested for a relationship between the genotype and such factors. Their findings indicated that the effect of the SNP rs143383 on OA was an independent one.

The effect of the SNP rs143383 was also examined in individuals with knee OA and controls. Among a Japanese population, the odds ratio of the susceptibility allele was 1.30 (95% CI 1.10–1.53), while among a Han Chinese population the odds ratio was 1.54 (95% CI 1.22–1.95).

Further analyses showed that the SNP rs143383 influences transcriptional activity in the core promoter of GDF5. It is hypothesized that increasing the expression of GDF5 or enhancing its downstream signal could be employed in strategies to prevent OA.

In conclusion, the authors state that their work will open a window for research into the etiology of OA and the development of more effective therapeutic agents.


Address for reprints: S Ikegawa, Laboratory for Bone and Joint Diseases, SNP Research Center, RIKEN, 4-6-1, Shirokanedai, Minato-ku, Tokyo 108-8639, Japan. Email: sikegawa@ims.u-tokyo.ac.jp

**Dissecting the heterogeneity of rheumatoid arthritis through linkage analysis of quantitative traits**

Criswell LA, Chen VW, Jawaeer D et al.


The results of this study showed quantitative trait linkage analysis in rheumatoid arthritis to be a powerful method for identifying novel genetic markers that might contribute to the pathology and heterogeneity of this complex disease.

Rheumatoid arthritis (RA) is a complex disease characterized by phenotypic heterogeneity and the contributions of multiple genetic and environmental factors that are still to be fully defined. In this study, the researchers analyzed potential linkage between quantitative RA traits – rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) autoantibody titers – and genetic loci.
A total of 1002 patients with RA from 491 multiplex families were recruited by the North American Rheumatoid Arthritis Consortium. Ninety-two percent of the patients were white and 77% were female. The mean age of the patients at RA diagnosis was 41 years and the mean disease duration was 14 years. Most of the patients had bone erosions (92%) and were positive for the human leukocyte antigen DRB1 shared epitope (SE; 84%). Patient DNA was genotyped for 379 microsatellite markers, resulting in 10-centimorgan genome-wide coverage. The genetic associations of serum RF and anti-CCP titers were assessed using the statistical package MERLIN (Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA); a non-parametric linkage analysis was employed because the values of both traits showed non-normal distributions.

The heritability of anti-CCP and RF titers was estimated to be 67% and 14%, respectively, suggesting a stronger influence of genetic factors on anti-CCP titer than on RF titer. The marker D6S1629 on chromosome 6p in the major histocompatibility complex showed the strongest evidence of linkage for both traits (logarithm of odds [LOD] score for anti-CCP 14.02; p<10\(^{-15}\); LOD score for RF 12.09; p<10\(^{-15}\)). Six other genomic regions with LOD scores >1.0 were found to be associated with both traits, on chromosome 1p21.1 (D1S1631), chromosome 5q15 (D5S1462), chromosome 8p23.1 (D8S277), chromosome 16p12.1 (D16S403), chromosome 16q23.1 (D16S516), and chromosome 18q21.31 (D18S858). Regions on chromosome 9p21.3 (D9S1121) and chromosome 16q23.1 (D16S516) showed evidence of linkage to anti-CCP titer, and regions on chromosome 5p15.2 (D5S817) and chromosome 1q42.3 (D1S235) showed evidence of linkage to RF titer. Similar genetic regions showed evidence of linkage to the presence of RA.

The linkage analysis was also performed after adjusting for several variables associated with each trait: sex and SE positivity for anti-CCP titer; and sex, disease duration, and exposure to tobacco smoke for RF titer. These adjustments influenced the results for both traits, indicating possible interaction between genes in particular regions and the specific covariate. Linkage analysis for RF titer was more strongly influenced by covariate adjustment, suggesting an important impact of non-genetic factors on the trait. Interestingly, sex had a strong impact on the linkage signal for both traits on chromosome 6p.

In conclusion, a genome-wide linkage analysis of quantitative traits in RA may be a promising tool to define novel genomic factors that contribute to the complex pathology of the disease.

---

**CARDIOVASCULAR RISK**

Hyperuricemia and incidence of hypertension among men without metabolic syndrome


In a clinical study that included 3073 men, it was shown that hyperuricemia increased the risk of developing hypertension by approximately 80%, independent of baseline blood pressure, renal function, serum lipid levels, body mass index, proteinuria, alcohol use, and age.

There is some evidence for an association between the level of serum uric acid and the risk of hypertension, but the causal relationship remains unclear – in particular, because of the frequency of other coexisting cardiovascular risk factors, such as the metabolic syndrome. To overcome the limitations imposed by overlapping risk factors, the investigators established a cohort study of men who were at risk of hypertension but who did not have elevated blood pressure, renal disease, diabetes, or the metabolic syndrome.

In this clinical trial, 3073 men with a mean age of 45.3 years were followed for approximately 6 years, with a response rate of >90%. The individuals were assessed for their medical and social history, including body mass index, blood pressure, lipid profile, blood glucose level, peripheral blood count, serum uric acid level, creatinine level, and alcohol and tobacco use. Hyperuricemia was defined as a serum uric acid concentration >7.0 mg/dL and hypertension was defined as a systolic blood pressure of >140 mmHg and a diastolic blood pressure of >90 mmHg.

Several statistical models were employed, with consideration of the aforementioned covariates, to examine the association between hyperuricemia and the incidence of hypertension. In a multivariate Cox regression model, baseline hyperuricemia increased the risk of hypertension when compared with normal serum uric acid levels (hazard ratio [HR] 1.81, 95% confidence interval [CI] 1.59–2.06; p<0.001). Using multivariate generalized estimating equations models, an increase in serum uric acid level was found to be associated with a significant increase in subsequent blood pressure (p=0.006).

Overall, there was a consistent and substantial risk for the development of hypertension among normotensive men with hyperuricemia at baseline. This observation may be linked to the potential association that hyperuricemia has with increased renal vascular resistance and salt retention.
Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled study

The term “metabolic syndrome” describes a constellation of cardiovascular risk factors such as atherogenic dyslipidemia, obesity, hypertension, and diabetes. In a case–control study from Crete (Greece), it was found that the prevalence of the metabolic syndrome in cases of rheumatoid arthritis (RA) was not increased. However, among patients with RA, the metabolic syndrome was more common in those with higher disease activity. This study suggests that reduction of disease activity is beneficial for patients’ cardiovascular risk profiles.

Patients with rheumatoid arthritis (RA; n=200, mean age 63 years) were compared with age- and sex-matched controls (n=400). The frequency of the metabolic syndrome was approximately 40% in both groups. The risk of having moderate-to-high disease activity was found to be significantly greater in patients with the metabolic syndrome than those without (odds ratio 9.24, 95% confidence interval 1.49–57.2).

The metabolic syndrome is considered to be a pro-inflammatory state in which expanded adipose tissue is the source of pro-inflammatory cytokines. The increased prevalence of the metabolic syndrome in patients with higher disease activity suggests the presence of a relationship between the two.

Prospective studies are necessary to test whether a direct interdependence exists between the metabolic syndrome and disease activity.

Atherosclerotic vascular events in a single large lupus cohort: prevalence and risk factors

Atherosclerotic events are more common in patients with systemic lupus erythematosus (SLE) than in those without. In an inception cohort of 561 patients, it was found that a combination of classic risk factors such as smoking contributed to atherosclerotic events in SLE. Neuropsychiatric involvement was the disease characteristic most strongly associated with the presence of atherosclerotic events.

Patients with systemic lupus erythematosus (SLE) have a five-fold increased risk of myocardial infarction and tend to develop vascular events at an earlier age than is seen in the general population.

In a total cohort of 1087 patients with SLE from Toronto (ON, Canada), the prevalence of atherosclerotic vascular events was 10.9%. Included in this total were 561 inception patients, who presented to the clinic within 12 months of diagnosis; 54 (9.6%) of these developed atherosclerotic events. Among the inception cohort, 54 matched controls were selected to enable investigation of risk factors and differences in disease expression in patients with and without atherosclerotic complications. All classic risk factors were present, but smoking was found to have the strongest effect. In addition, the study revealed that treatment of risk factors not only reduced the occurrence of atherosclerotic events but also decreased the risk of developing neuropsychiatric SLE.

Address for reprints: MB Urowitz, Toronto Western Hospital, 399 Bathurst Street, 1E-410B, Toronto, ON, M5T 2S8, Canada. Email: m.urowitz@utoronto.ca

Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis

In this retrospective chart review, the presence of extra-articular disease in patients with rheumatoid arthritis was found to be an independent risk factor for the occurrence of a cardiovascular event.

Rheumatoid arthritis (RA) is associated with an increased mortality rate relative to that seen in the general population, and extra-articular disease has been shown to be one of the predictors of the increase. Much of the excess mortality in RA is attributable to cardiovascular disease. In this study, 81 patients with extra-articular RA were compared with 184 control patients. Records were reviewed for the first occurrence of a cardiovascular event.

In univariate analysis, age, male sex, smoking, positive rheumatoid factor status, erosive disease, and severe extra-articular disease were all predictors of a first cardiovascular event. Extra-articular disease, in particular, was associated with coronary artery disease, cerebrovascular disease, and any cardiovascular event. After controlling for all potential variables, age, male sex, and extra-articular disease remained predictors of a first cardiovascular event.

This study of patients with RA included in a database from a tertiary referral center suggests that severe extra-
articular disease is an independent risk factor for cardiovascular events in this population. The presence of rheumatoid factor and erosive disease failed to remain statistically significant risk factors after multivariate analysis, suggesting that extra-articular involvement is not simply a marker for disease severity. Other studies have revealed the inability of traditional cardiovascular risk factors to entirely explain the excess cardiovascular mortality rate in RA. Future prospective studies may help to explain exactly how disease-specific factors such as extra-articular involvement may contribute to this excess mortality rate.

Address for reprints: C Turesson, Department of Rheumatology, Malmo University Hospital, Sodra Forstadsgatan 101, S-205 02 Malmo, Sweden. Email: turesson.carl@mayo.edu
The American College of Rheumatology’s *Innovative Therapies in Autoimmune Diseases Conference* (held in Washington, DC, USA, on March 2–4, 2007) provided a unique opportunity for rheumatology clinicians and investigators, pharmaceutical industry researchers, and regulatory personnel to share their perspectives on the development and assessment of rheumatological therapeutics.

The meeting opened with a morning session on the mechanics of clinical trials and drug development. Aimed primarily at trainees, the session attracted a large audience of clinicians interested in learning more about the research process leading to registration of new agents.

Session one
The first session of the main meeting was a full Friday afternoon focused on tools used to ensure that the right populations are targeted in clinical trials and clinical practice, including surrogate outcomes, biomarkers, and genetic markers. Maarten Boers (VU University Medical Center, Amsterdam, The Netherlands) opened the session with a discussion of surrogate outcomes, highlighting the nomenclature and stressing the need to avoid using terms interchangeably. For example, biomarkers are disease-centered variables that may not necessarily predict outcome and may even serve as risk factors to predict prognosis. Only when biomarkers are definitively linked to patient or clinical outcomes can they be considered surrogate outcomes. Professor Boers then reviewed the levels of evidence necessary to consider a biomarker a surrogate. Ronenn Roubenoff (Biogen Idec, Cambridge, MA, USA) and Steven Cummings (San Francisco Coordinating Center, San Francisco, CA, USA) followed with lectures on the development of biomarkers and their use in specific clinical conditions, such as osteoporosis, including magnetic resonance imaging, ultrasound, and conventional radiography, as biomarkers for rheumatoid arthritis (RA) and osteoarthritis. Robert Plenge (Brigham and Women’s Hospital, Boston, MA, USA) highlighted the use of genetic analysis as a tool to identify disease activity and prognosis. Finally, Jeffrey Siegel, of the US Food and Drug Administration, discussed the use of alternative trial designs, including enrichment methods using biomarkers to target appropriate populations, and adaptive study protocols that may facilitate drug development without sacrificing the validity of the results. A panel discussion concluded the afternoon, generating a lot of input from the audience on the ways in which biomarkers might be used to improve clinical research and practice.

Session two
The second session, on Saturday morning, focused on drug safety, exploring ways to learn from previous lessons and to acquire better safety information in the future. E William St Clair (Duke University Medical Center, Durham, NC, USA) opened with a lecture on “learning from the literature,” which covered the use of available preclinical data to better predict the toxicities likely to be seen during clinical trials. E William St Clair (Duke University Medical Center, Durham, NC, USA) opened with a lecture on “learning from the literature,” which covered the use of available preclinical data to better predict the toxicities likely to be seen during clinical trials. He cited three examples of published preclinical data that heralded toxicities later seen in clinical trials – tuberculosis reactivation with tumor necrosis factor (TNF) inhibition, cytokine release syndrome triggered by monoclonal antibody binding, and Epstein–Barr virus reactivation with T cell inhibition. Nicki Panoskaltsis (Imperial College London, London, UK) followed with an example of the recent clinical trial of the superagonist TGN1412, in which preclinical experiments appeared to have failed to prevent catastrophic toxicity in six volunteers. Her presentation sparked a heated discussion among the audience and other presenters on study designs and procedures for the Phase I investigations that might have avoided the unfortunate outcome. Kevin L Winthrop (California Department of Health Services, Sacramento, CA, USA) gave a talk on assessing the infectious complications of biological therapies and opened a
broader discussion on the coordination of pre- and post-approval evaluation of drug toxicity. Joel Kremer (The Center for Rheumatology, Albany, NY, USA) expanded on this issue with a review of the role of registries in following post-marketing safety. Lectures by Fred D Lublin (Mount Sinai Medical Center, New York, NY, USA) on the risk of progressive multifocal leukoencephalopathy seen post-marketing with natalizumab and by Claire Bombarider (Institute for Work and Health, Toronto, ON, Canada) on the cardiovascular toxicity that led to the withdrawal of rofecoxib from the US market led into a panel discussion on the ways in which the drug approval process could be modified to reduce the risk of similar events in the future. There was some agreement among the panel and the audience that tighter oversight of safety during the initial marketing period, perhaps including a form of conditional approval, is warranted.

Session three
Saturday afternoon’s session focused on systemic lupus erythematosus (SLE), a disease that seems poised to see the same explosion of available and effective therapies that has been witnessed in RA over the last 10 years. The session opened with introductory lectures by Jennifer Grossman (University of California – Los Angeles, Los Angeles, CA, USA) and Dafna D Gladman (Toronto Western Hospital, Toronto, ON, Canada) on defining disease subsets and appropriate outcome measures for SLE trials. Vibeke Strand (Stanford University, Palo Alto, CA, USA) followed with a discussion of the difficulties of trial design in a disease with so many different potential manifestations. The session continued with a series of short talks highlighting current research and development plans for a variety of novel therapies for SLE – including abatacept (cytotoxic T lymphocyte-associated antigen-4 immunoglobulin), belimumab (anti-B lymphocyte stimulator), epratuzumab (anti-CD22 antigen), and rituximab (anti-CD20 antigen) – and concluded with a review by Bevra H Hahn (University of California – Los Angeles) of the current status of stem-cell transplantation for SLE.

Session four
The final session, on Sunday morning, comprised a series of lectures on unique aspects of innovative therapies. Charles Serhan (Brigham and Women’s Hospital) discussed the lipidome – the complex of molecules in the lipid metabolic pathway – and its relevance to the treatment of inflammatory diseases. He introduced the concept of resolution of inflammation as an active process and described compounds, such as lipoxin and resolvin, that appear to play a role in the process and may therefore be targets for future therapeutic development. David E Szymkowski (Xencor, Inc., Monrovia, CA, USA) discussed the development of a novel compound, the dominant-negative TNF. This mutated form of TNF, which has no agonist activity, intercalates into the trimeric structure of native TNF and disrupts its biological activity. Gary S Firestein (University of California – San Diego, La Jolla, CA, USA) reviewed the current state of knowledge on signal transduction as regards its application to potential therapies for rheumatic diseases. He discussed the difficulties inherent in targeting these kinase pathways and proposed a number of modified approaches that may be able to limit toxicity by focusing the effects of these agents.

Joan M Bathon (Johns Hopkins University, Baltimore, MD, USA) led a provocative discussion on the complexities of conflicts of interest in therapeutic research. She stressed that individual researchers need to regularly examine their own relationships with industry; audience members pointed out that academic institutions are not immune to conflicts either. Leonard H Calabrese (Cleveland Clinic Foundation, Cleveland, OH, USA) delivered the final lecture, on the relationship between hepatitis B and C and the rheumatic diseases and their therapies. The meeting chairs, Edward Keystone (Mount Sinai Hospital) and Daniel Furst (University of California – Los Angeles), closed the session with a summary of some of the meeting’s highlights and noted that planning has begun for the next meeting, to be held in the spring of 2009.
### SEPTEMBER

**5–14**  
**14th PreS Congress**  
Istanbul, Turkey  
Contact: Congress Secretariat  
E pres2007@flaptour.com.tr  

**6–8**  
**UCSF Rheumatology Board Review 2007**  
San Francisco, CA, USA  
Contact: UCSF Office of Continuing Medical Education  
T +1 415 476 4251  
+1 415 476 5808  
F +1 415 476 0318  
+1 415 502 1795  
E info@ocme.ucsf.edu  
W www.cme.ucsf.edu

**15–18**  
**Advances in Rheumatology**  
Boston, MA, USA  
Contact: Harvard Medical School CME Office  
T +1 617 384 8600  
F +1 617 384 8686  
E hms-cme@hms.harvard.edu  
W cme.med.harvard.edu

**19–22**  
**35th Congress of the German Society for Rheumatology**  
Hamburg, Germany  
Contact: Martin Berndt  
T +49 211 585 897 0  
F +49 211 585 897 99  
E info.duesseldorf@intercongress.de  
W www.intercongress.de

**23–26**  
**3rd International Clinical Trials Symposium**  
Sydney, NSW, Australia  
Contact: Sandra Ibrahim  
T +61 2 954 5000  
F +61 2 925 13552  
E info@clinicaltrials2007.com  
W www.clinicaltrials2007.com

**27–30**  
**American Academy of Pain Management Annual Conference**  
Las Vegas, NV, USA  
Contact: Jillian Manley  
T +1 209 533 9744  
F +1 209 533 9750  
E jillian@aapainmanage.org  
W www.aapainmanage.org

**29 September–2 October**  
**7th World Congress of the International Cartilage Repair Society**  
Warsaw, Poland  
Contact: Stephan Seiler  
T +41 443 901 840  
F +41 443 901 841  
E sseiler@cartilage.org  
W www.cartilage.org

### OCTOBER

**2–6**  
**EuroSpine 2007**  
Brussels, Belgium  
Contact: Werner Van Cleemputte  
T +32 093 443 959  
F +32 093 444 010  
E eurospine@medicongress.com

**4–6**  
**4th Multidisciplinary Congress: A Clinical and Rehabilitative Approach to Rheumatology**  
Mantova, Italy  
Contact: Andrea Rossetti  
T +39 0523 335 732  
F +39 0523 334 997  
E reumantova@euroconventions.it  
W www.euroconventions.it/reumantova

**6–13**  
**Rheumatology & Chronic Pain CME Cruise**  
Papeete, French Polynesia  
Contact: Sea Courses Cruises  
T +1 888 647 7327  
F +1 888 547 7337  
E cruises@seacourses.com  
W seacourses.com

---

**If you would like your meeting listed here, please contact the Publisher (for details see inside front cover).**