Reactive Arthritis

Reaktive Arthritis

J. Braun^{1,2}, J. Sieper¹

Summary: The clinical picture of reactive arthritis is characterized by an asymmetric oligoarthritis of the lower limbs and a preceding infection in the gut or the urethra. Diagnostic criteria for reactive arthritis rely mainly on such clinical features but one should try to identify the causative microbe. Stool cultures are rarely positive but urethral smears and urine examinations by PCR can be helpful. Serology is mostly too nonspecific and partly not sensitive enough. The microbiological results have to be carefully interpreted – especially since there is no indication that a positive result should have therapeutic consequences such as antibiotic therapy. Studying the immunologic mechanisms that cause reactive arthritis is essential also for the pathogenesis of other spondyloarthropathies such as ankylosing spondylitis. The details of the interplay between bacterial antigens and HLA-B27 have become somewhat clearer in recent years. There is some evidence for longer bacterial persistence in the joints and there is a local antigen-specific immune response in which CD4⁺ and CD8⁺ T cells seem to play a role, immunodominant antigens and peptides have been identified. Furthermore, there seems to be a distinct cytokine pattern in reactive arthritis which is more TH2 like. The prognosis of reactive arthritis patients is influenced by the ability of the patients to secrete TNF- α . There seems to be a link between TNF polymorphisms and HLA-B27.

Keywords: Arthritis, Reactive/immunology; Arthritis, Reactive/etiology; Arthritis, Reactive/epidemiology.

Zusammenfassung: Das klinische Bild einer reaktiven Arthritis (ReA) ist charakterisiert durch eine asymmetrische Oligoarthritis der unteren Extremitäten und eine vorhergehende Infektion des Darmes oder der Urethra. Die diagnostischen Kriterien für ReA basieren vor allem auf diesen klinischen Zeichen, es sollte jedoch der Versuch gemacht werden, die auslösende Mikrobo zu identifizieren. Während Stuhlkul-

turen selten positiv ausfallen, können Urethralabstriche und Urinuntersuchungen mit der Polymerase-Kettenreaktion hilfreich sein. Die Serologie ist meistens zu unspezifisch und in einigen Fällen auch zu wenig sensitiv. Mikrobiologische Befunde sind mit Vorsicht zu interpretieren, da es keinen Hinweis gibt, daß positive Befunde zu therapeutischen Konsequenzen wie Antibiotikatherapie führen. Die Abklärung der immunologischen Mechanismen, die eine ReA bedingen, ist auch für die Pathogenese anderer Spondyloarthropathien wie die ankylosierende Spondylitis essentiell. Die Einzelheiten der Wechselwirkung zwischen bakteriellen Antigenen und HLA-B27 sind in den letzten Jahren etwas klarer geworden. Es gibt Anzeichen für längere bakterielle Persistenz in den Gelenken. Eine lokale antigen-spezifische Immunantwort, bei denen CD4⁺ und CD8⁺ T Zellen eine Rolle zu spielen scheinen, sowie immundominante Antigene und Peptide konnten identifiziert werden. Weiterhin scheint es ein abgrenzbares TH2-ähnliches Cytokinmuster bei der ReA zu geben. Die Prognose der ReA wird von der Fähigkeit des Patienten zur Sekretion von Tumornekrosefaktor α (TNF- α) beeinflusst. Es scheint eine Verbindung zwischen TNF Polymorphismen und HLA-B27 zu bestehen.

Schlüsselwörter: Arthritis, Reaktive/Immunologie; Arthritis, Reaktive/Ätiologie; Arthritis, Reaktive/Epidemiologie.

Reactive arthritis (ReA) occurs after preceding bacterial infections of the gut or the urogenital tract. ReA has attracted considerable interest in rheumatology and immunology

- (i) because a causative bacterial antigen can be identified,
- (ii) because of its association with HLA-B27 and
- (iii) due to its link to the whole spectrum of spondyloarthropathy.

The term reactive arthritis refers to an inflammatory arthropathy following infections at sites apart from joint structures with a wide spectrum of microbes. These organisms can, per definitionem, not be cultured from joint material. The most relevant form of ReA comprises an arthritis after a preceding infection of the urogenital tract with *Chlamydia trachomatis* or of the gastrointestinal tract with enterobacteriae such as *Yersinia*, *Salmonella*, *Shigella* and *Campylobacter*.

Based on a lecture at the symposium "Systemic and organ-related auto-immune diseases: A challenge for the medical laboratory" at the Congress of Laboratory Medicine in Duesseldorf, Germany, on November 16, 1998

¹Department of Medicine, Rheumatology, University Hospital Benjamin Franklin, Berlin, Germany

²Correspondence to: Dr. med. Jürgen Braun, Department of Medicine, Rheumatology, University Hospital Benjamin Franklin, Hindenburgdamm 30, D-12200 Berlin, Germany. Fax: +49-30- 8445-4582; E-mail: jbraun@zedat.fu-berlin.de

Received: February 25, 1999

The characteristic clinical feature of ReA is an asymmetric arthritis predominantly of the lower limbs and, partly, overlap and transition to other spondyloarthropathies such as ankylosing spondylitis. A considerable number of patients with ReA might also present under the clinical picture of undifferentiated oligoarthritis or undifferentiated spondyloarthropathy - these are cases without symptomatic preceding infection in which no evidence for involvement of a bacterial antigen could be found.

In this article we review the most recently published reports on different aspects of ReA with some impact on its pathogenesis, diagnosis and epidemiology.

Pathogenesis

The two most central findings for the pathogenesis of ReA which have been published by different groups in recent years provide evidence that bacteria or bacterial products are present in the joint and that a local immune response is directed against these bacteria [1, 2].

Detection of bacterial DNA by PCR technique

More evidence has recently been accumulated that *Chlamydia trachomatis* persists alive in the joint. Wilkinson et al. [3] reported that *Chlamydia trachomatis* can be detected not only in ReA but also in about 30% of patients with undifferentiated oligoarthritis in synovial fluid (SF), a figure similar to earlier studies [4]. In contrast, *Chlamydia pneumoniae* was not found in these patients. Thus, despite earlier reports about the occasional detection of *C. pneumoniae* in SF [5, 6] this bacterium seems to be less relevant as a triggering pathogen for ReA.

Not only chlamydial DNA but also mRNA has been found in synovial membrane biopsies; this can be taken as strong evidence that Chlamydia do persist alive in vivo [7]. Most interestingly, a transcript for omp1, the major outer membrane protein from Chlamydia which is the major target for the humoral immune response, was not detected but transcripts for other chlamydial proteins such as the heat shock protein (hsp) 60 were found [7]. Thus, in a latent form, Chlamydia seems to express different proteins compared to an active form.

The situation seems to be different for enterobacteria. Most attempts looking for bacterial DNA in the joint by PCR have failed in the past [8]. Only recently *Campylobacter jejuni* [6] and *Yersinia enterocolitica* [9] have been found occasionally in the joint by PCR techniques. Salmonella could be detected in the joint

by various other methods but not by PCR in one study [10] while a weakly positive result in a single patient was reported from Finland (K. Granfors, personal communication).

Taken together, current knowledge suggests that *Chlamydia trachomatis* DNA can be repeatedly found in the joint in a substantial portion of patients indicating that Chlamydia do persist alive in these structures. Of interest, a direct comparison between synovial fluid and - membrane revealed a higher sensitivity of the latter [11]. In contrast to Chlamydia, the detection of enterobacterial DNA by PCR has been much more difficult - despite the documentation of bacterial products such as lipopolysaccharide (LPS) in the joint. This suggests that enterobacteria persist elsewhere. However, enterobacteria seem to survive in vivo as indicated by the finding of Yersinia heat shock protein in synovial fluid and peripheral blood cells of ReA patients for up to 4 years [12]. For a shorter time period, these antigens were also detected in peripheral blood cells of patients with Yersinia enteritis who did not develop ReA. These results are backed by older reports from the same group showing that anti-Yersinia-IgA persists in ReA patients for up to 2 years. This would be unlikely if Yersinia were dead or had been cleared [13]. As a possible site for persistence the gut mucosa or locations nearby have been suggested. Using PCR also *Chlamydia trachomatis* has been detected in peripheral blood cells but not in the serum of 2 patients with early Chlamydia-induced ReA [14]. This finding makes it likely that Chlamydia is transported intracellularly via the blood to the joints.

Two studies have also tried to screen for new bacteria in the joint using universal 16S ribosomal primers with subsequent DNA sequencing in case of positivity [9, 15]. Besides expected microbes such as *Chlamydia trachomatis*, *Yersinia enterocolitica* was detected for the first time in an arthritis patient with preceding diarrhea in one study [9]. However, also ubiquitous pathogens such as Pseudomonas, Acinetobacter and even Mycobacteria were detected in various forms of arthritides. It remains to be shown whether these bacteria are of any pathogenetical relevance or whether they are just innocent bystanders.

Antigen specific T cell responses and cytokine secretion

In the study by Wilkinson et al. [3] an inverse relationship between the presence of chlamydial DNA in the joint and the synovial Chlamydia-specific lymphocyte proliferation was found. This suggests that an impaired T cell response might contribute to the persistence of bacteria. This hypothesis is backed by two studies from our lab. When synovial T cells from ReA patients were stimulated in vitro with the triggering bacteria the IFN γ /IL10 ratio and the TNF- α /IL10 ratio were clearly lower [16] compared to the response to *Borrelia burgdorferi* in Lyme arthritis patients [17]. Because cytokines such as IFN γ and TNF- α are crucial for the

Non standardized abbreviations: CD, cluster designation; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; LCR, ligase chain reaction; LPS, lipopolysaccharide; PCR, polymerase chain reaction; ReA, reactive arthritis; TNF, tumor necrosis factor; UOA, undifferentiated oligoarthritis.

elimination of bacteria such as *Yersinia* and *Chlamydia* the insufficient production of these cytokines in ReA patients might contribute to bacterial persistence. Especially TNF- α seems to be relevant. In 55 patients with early ReA (disease duration less than 8 weeks) peripheral blood mononuclear cells secreted significantly less TNF- α upon mitogenic stimulation than 30 patients with early untreated rheumatoid arthritis [18]. Furthermore ReA patients with a lower TNF- α -secretion had a longer disease duration than patients with a higher secretion. Such a low TNF- α -production might be, at least partly, genetically determined. Hhler et al. reported that in ankylosing spondylitis patients the TNF2 variant which has been associated with high levels of TNF- α production is underrepresented compared to controls [19]. Taken together, these results suggest that bacteria persist in ReA as a consequence of an insufficient immune response.

The question which bacterial antigens are at all and preferentially seen by synovial T cells has been addressed by several studies. Most interestingly, similar to the already cited expression of chlamydial hsp60 in the synovial membrane this heat shock protein seems to be also important for the synovial T cell response. A DR4-restricted T cell epitope within the chlamydial hsp60 has been described which was identical for *Chlamydia trachomatis* and *Chlamydia pneumoniae* but was not cross-reactive with the enterobacterial hsp60 or the human hsp60 [20]. Thus, the immune response against the chlamydial hsp60 seems to be important for the pathogenesis of *Chlamydia* induced arthritis but this cannot explain the similarity with enteric ReA.

Another study investigated which of several recombinant *Yersinia* proteins were recognized by synovial CD4⁺ T cells from patients with *Yersinia*-induced ReA [21]. A few proteins including the 19kd urease β subunit were able to stimulate the local T cells. However, the strongest proliferative response was induced by the *Yersinia* hsp60. T cell clones derived from one patient were further investigated. One clone responding to a hsp60 of different origin including the human 60kd showed a T helper (h) 2-like cytokine secretion pattern while another clone which recognized specifically only the *Yersinia* hsp60 showed a more Th1-like pattern. This indicates that two types of T cells seem to be present in the joint. We hypothesize that the one with the Th1-pattern is probably able to fight *Yersinia* effectively while the Th2-clones might promote bacterial persistence. The presence of both types suggests that there is a therapeutic chance to change the balance.

Synovial CD8⁺ T cells from patients with HLA-B27-positive *Yersinia*-induced ReA were shown to recognize only peptides derived from the *Yersinia* hsp60 but not from other *Yersinia*-derived proteins [22]. A single hsp60-derived peptide (321-329) could be identified as the immunodominant antigen seen in an HLA-B27 restricted fashion by synovial CD8⁺ T cells from 3 different patients. The hsp60 from other

enterobacteria contains the same peptide sequence but the chlamydial and human ones are different. This first identification of an HLA-B27 restricted T cell response to a bacterial peptide now allows us to look for cross-reacting peptides derived from other bacteria or from human proteins. Most interestingly, we have recently identified an immunodominant peptide for CD4⁺ T cells from the *Yersinia* hsp60 which is located in the very same area of the protein as the CD8 epitope [23].

Further support for the arthritogenic peptide hypothesis which claims that a bacterial or a self peptide is presented by HLA-B27 to CD8⁺T cells is given by a recent study of Joel Taurog's lab [24]. A minigene construct for a peptide derived from the influenza nucleoprotein which is known to bind to HLA-B27 with high affinity was transfected into SpA-susceptible HLA-B27 transgenic rats. These rats had a significantly reduced prevalence of arthritis compared to control animals suggesting that B27-related arthritis requires binding of a specific peptide by HLA-B27. Thus, pathogenic peptides could be efficiently substituted by a stronger binding peptides. This could be an exciting new approach for treating chronic courses of HLA-B27-associated disease.

In humans, the T cell response in ReA was recently examined by Fendler and colleagues who reported that a bacteria-specific lymphocyte proliferation was also detectable in peripheral blood of 45% of the patients if investigated between weeks 2 and 4 after the onset of arthritis [25]. In another study the same authors demonstrated that in arthritis triggered by *Chlamydia*, *Shigella* or *Borrelia burgdorferi* the same triggering bacterium was recognized by synovial lymphocyte proliferation when synovial fluid bulk cultures were investigated longitudinally, only the response to *Yersinia* seems to be partly non-specific [26]. Both, CD4⁺ and CD8⁺ T cells, analysed by three colour flow cytometry, showed evidence of recent activation in ReA patients [27].

Inman introduced an interesting new animal model for *Chlamydia trachomatis*-induced arthritis in male Lewis rats [28]. When synoviocytes infected with *Chlamydia trachomatis* were injected into the knee joints of these rats they developed an acute arthritis with the detection of live *Chlamydia* in the joint. The chronic phase was characterized by mononuclear cell infiltrations in the absence of culturable *Chlamydia*. Therefore, this model is somewhat similar to the situation in humans and might serve as a model for addressing further questions regarding pathogenesis and treatment.

In contrast to earlier reports HLA-B27 expression on the cell surface did not influence the invasion of *Salmonella* or *Yersinia* [29]. However, Laitio et al. reported that the intracellular elimination of *Salmonella* was inhibited in HLA-B27 positive cells in contrast to HLA-B27-negative cells [30]. It remains to be seen whether such a mechanism could be relevant for the pathogenesis of the HLA-B27-associated diseases.

Epidemiology

It is generally assumed that the prevalence of the whole group of the spondyloarthropathies is underestimated because the diagnosis is often not easy, especially for ReA and undifferentiated spondyloarthropathy. In a communitywide epidemiologic study *Boyer et al.* could show that 72% of the community cases had not been diagnosed as spondyloarthropathy previously and 36% of the ReA patients had not been correctly classified [31]. In a prevalence study on spondyloarthropathies which was performed by investigating HLA-B27-positive and -negative blood donors we have recently reported that the overall prevalence of spondyloarthropathy can be calculated as high as 13.6% among HLA-B27-positives and 1.9% in the general population [32]. The most frequent diagnosis were undifferentiated spondyloarthropathy and ankylosing spondylitis. The prevalence for ReA which in the majority of cases runs a self limiting course was calculated as 0.1%. In an earlier study the annual incidence was reported to be about 10/100000 for ReA [33].

In a recent report on an outbreak of gut infections with *Salmonella Bovismorbificans* in 210 patients in Finland [34] 12% developed ReA; there were no significant differences between children (8%) and adults (12%). Forty-five percent of the ReA patients were HLA-B27-positive. In contrast to earlier studies the duration and severity of ReA did not differ between HLA-B27-positive and -negative patients.

Diagnosis and treatment of reactive arthritis

The difficulties of diagnosing ReA have recently been highlighted by *Pacheco-Tena et al.* who analyzed the ReA literature showing that most authors are using their own diagnostic criteria [35]. Thus, an agreement on and an evaluation of diagnostic criteria such as those recently proposed [36] is urgently needed as discussed in a recent editorial [37].

For diagnosis it is essential to demonstrate a link between a preceding bacterial infection of the gut or the urogenital tract and the arthritis. This is easy if the triggering infection is symptomatic such as a diarrhea or urethritis/cervicitis and if the bacterium can be detected in the stool or the urogenital tract. However, this is rarely the case because (i) the preceding infections are often clinically mild or even asymptomatic and (ii) the bacteria are only rarely detected at the site of the initially infection at the time when arthritis occurs or when the patient is seen by a rheumatologist.

Earlier sets of diagnostic criteria have almost exclusively relied on clinical symptoms such as a preceding symptomatic diarrhea or urethritis or extraarticular manifestations such as involvement of the eye, skin or mucosa [38-40]. This is also true for those criteria

which are part of the classification criteria for the whole group of spondyloarthropathies [41].

With improvements in the techniques for the detection of antibacterial antibodies and with a more precise definition of bacterial target antigens for a humoral immune response serology has been increasingly used for diagnosis of ReA and for identification of the causative bacterium. Only recently the highly sensitive method of polymerase chain reaction has been introduced for the detection of bacterial DNA [3, 4].

The exclusive use of clinical criteria to diagnose reactive arthritis [38-40] has limitations and identification of the triggering bacterium should be tried for scientific reasons because otherwise (i) the differentiation between ReA and undifferentiated spondyloarthropathy becomes difficult; (ii) many cases of ReA which present solely with peripheral arthritis without extra-articular symptoms (most probably the majority) are not diagnosed; (iii) for a better understanding of the pathogenesis and (iv) because there are probably different options of treatment for different causative bacteria [42].

Diagnostic criteria for reactive arthritis have been proposed at the 'Third International Workshop on Reactive Arthritis' (Table 1). These should be evaluated by a group of experts at the next workshop which will take place in Berlin in July 1999 - based on clinical symptoms, on the course of the arthritis, on anti-bacterial serology (discussed below), on stool culture results, and detection of *Chlamydia trachomatis* in the urine and synovial fluid/synovial membrane by PCR (Table 2). There is also need to investigate whether the diagnosis of ReA should be limited to a disease duration of 4-6 weeks or not and whether it helps to differentiate between acute and chronic ReA.

Serology in reactive arthritis

As far as serology is concerned most information is available for *Yersinia*, *Salmonella* and *Chlamydia trachomatis*. Specific and sensitive tests using bacteria-specific LPS or other antigens for the identification of antibodies directed against *Yersinia* or *Salmonella* have been introduced and investigated in the past [43-46].

The determination of antibacterial IgG-antibodies is not sufficient because these antibodies can persist for months or even years after clearance of bacteria. In contrast, the detection of bacterium-specific IgM- or IgA-antibodies is known to indicate a recent or persistent infection. IgA-antibodies have a short half life and should be only present if constantly stimulated by microbes in the mucosa. The Widal agglutination test detects IgM-antibodies and can therefore be used to prove a recent bacterial infection. This test is currently used for *Yersinia* and, if positive, can be used as a hint to diagnosis. In the case of *Salmonella* its sensitivity is too low; this is especially problematic in acute infections [46].

Although serology is widely used for the diagnosis of ReA its value is not clear because of an unknown

Table 1 Diagnostic criteria for reactive arthritis*. Other rheumatic diseases should be excluded.

- Asymmetrical arthritis predominantly of the lower limbs plus
- Evidence of preceding infection**

*based on the results of the 3. International Workshop on Reactive Arthritis

**for more details see Table 2

Table 2 Diagnosis of reactive arthritis: clinical manifestations or laboratory tests as evidence for preceding infections

- Clinical diarrhea or urethritis within preceding four weeks
- Positive stool culture
- Detection of *Chlamydia trachomatis* in the first portion of the morning urine (LCR)
- Detection of *Chlamydia trachomatis* by urethral/cervical smear
- Yersinia- or Salmonella-antibodies against lipopolysaccharide or other specific antigens of IgG- plus IgA- or IgG- plus IgM-subtype[#]
- Sensitivity and specificity of serology to detect chlamydial infections is currently too low
- Detection of chlamydial DNA in the joint by PCR technique

* The sensitivity, specificity and the positive predictive value of the single criteria and various combinations of criteria should be evaluated in a prospective study.

[#] Serology for *Campylobacter jejuni* and *Shigella* in the diagnosis of reactive arthritis has still to be established.

specificity and sensitivity. Bas et al. investigated the humoral immune response to *Chlamydia trachomatis* in patients with Chlamydia-induced ReA. They found evidence for a local anti-Chlamydia IgA-production in synovial fluid [50]. When investigating the value of serotype determination of serum antibodies against whole Chlamydia they reported that only very high values of specific isotypes were helpful for the diagnosis of Chlamydia-induced ReA and that the best sensitivity (63%) was obtained for specific IgM-antibodies and/or IgA-antibodies with a specificity of 81% [48]. In a subsequent study the same authors investigated the role for an ELISA-test using recombinant forms of chlamydia proteins or single Chlamydia-derived peptides [49]. A differentiation between *Chlamydia trachomatis* and *Chlamydia pneumoniae* could be made based on these tests. Although the sensitivity of IgG and IgA anti-MOMP or anti-LPS antibodies were high the specificity was quite low due to a high number of positive results in controls. A relatively high specificity and sensitivity of about 80% was observed

for IgG anti-MOMP antibodies present in the synovial fluid. However, taken together, at the moment no clear recommendation for the use of chlamydial serology can be made.

Although the sensitivity and the specificity of such tests to detect an infection has been improved the question arises how sensitive and specific they are for the diagnosis of ReA [47]. Our Finnish colleagues have studied patients with Yersinia- or Salmonella-induced ReA for up to 2 years in whom the triggering bacterium was initially identified by a positive stool culture. They could nicely demonstrate that in Yersinia-induced ReA IgG- plus IgA-antibodies persisted for months and even years [44] while in Salmonella-induced ReA persistence of IgG-, IgM- and IgA-antibodies was found [46]. Furthermore, in patients with ReA antibody titers were higher and persisted longer compared to patients with infectious enteritis without the complication of arthritis. Current knowledge therefore suggests that the sensitivity of these tests, based mainly on bacteria-specific LPS antigens, is relatively high for the diagnosis of ReA.

Another problem concerns the specificity of these tests for the diagnosis of enteric ReA. Based on investigations of epidemics of infectious enteritis it can be assumed that about 2-4% of these patients do develop ReA while this figure goes up to 20-25% if the individuals are positive for HLA-B27. This means that the great majority of antibody-positive patients do not get arthritis. Such a percentage most probably differs from country to country due to genetic (in addition to HLA-B27) and environmental influences [45]. The specificity of such a test is determined by the prevalence of a positive serology in the local population which might also be different between countries [43]. However, although a high prevalence of antibacterial antibodies in the normal population could reduce specificity and therefore the positive predictive value (PPV) [50], a higher prevalence of infections could also result in a higher prevalence of ReA and therefore in an increase of the PPV.

The positive predictive value for Yersinia- and Salmonella-serology for the diagnosis of ReA is not clear at the moment because a golden standard is lacking. Unfortunately, as discussed above, detection of DNA from enterobacteriae in the joint by PCR has mostly failed [8,10]. Much less information is currently available on the value of serology in the diagnosis of *Campylobacter jejuni*-induced or *Shigella*-induced ReA; both do not seem valid for practical usage.

The clinical picture and the course of the arthritis is similar in enteric and Chlamydia-induced ReA, but some aspects differ. (i) Although antibodies against the different Chlamydia species (*C. trachomatis*, *C. pneumoniae* and *C. psittaci*) can be differentiated serologically, the best test for this has yet to be established, at the moment the microimmunofluorescence test seems to be advantageous. (ii) A substantial proportion of patients with Chlamydia-induced ReA can be antibody-negative indicating a low sensitivity [4,9]. (iii) A much

higher percentage of normal control populations is positive for IgG plus IgA or IgG plus IgM antibodies compared to enterobacteria indicating a low specificity. High antibody titers correlated best with correct diagnosis in a recent study [49]. (iv) *Chlamydia trachomatis* can be detected in the urogenital tract much more frequently than bacteria in the stool at the time of arthritis and it can now be found much more easily and reliably in the first portion of the morning urine (instead of performing a swab from the urogenital tract). Therefore, this method should be part of a diagnostic approach although its specificity can be reduced if a high number of positive cases can be found in the normal population as has recently been reported in young female recruits [51]. (v) Finally, chlamydial DNA can be detected in the joint (synovial fluid and synovial membrane) by PCR technique [7, 11] which should therefore also be included in a diagnostic work up for scientific purposes.

Treatment of reactive arthritis with antibiotics

As a consequence of the presence of live *Chlamydia* in the joint and because survival of enterobacteria is assumed to happen outside the joint it is a crucial question whether antibiotic therapy can shorten the disease duration and is able to cure chronic ReA patients. In a recent double-blind study more than 100 patients diagnosed as either ReA or undifferentiated oligoarthritis (UOA) were treated for 3 months with 1000 mg/day of ciprofloxacin or placebo [52]. Ciprofloxacin was not superior to placebo in ReA and UOA patients. This was especially true for the patients in whom enterobacteria had been identified as the triggering bacteria. In contrast, ciprofloxacin seemed to be somewhat better than placebo in patients with *Chlamydia*-induced arthritis. However, this difference was not significant because of the small number of patients in this group.

A negative result of antibiotic treatment for enteric ReA and a possibly positive for *Chlamydia*-induced ReA is in line with the earlier tetracycline study by *Lauhi* et al. [53]. In contrast to these studies *Wollenhaupt* et al. did not see an effect of doxycycline therapy over 4 months in patients with *Chlamydia*-induced arthritis [54]. The disease duration was longer than 6 months in this study. Therefore, it seems logical to perform a larger antibiotic study concentrating on patients with *Chlamydia*-induced arthritis as recently suggested [55]. While treatment of a urogenital tract infection due to *Chlamydia trachomatis* with antibiotics seems to be effective in preventing the occurrence of ReA [56] this did not work in *Salmonella*-induced enteritis as confirmed in a Finnish investigation of a *Salmonella* outbreak [55]. Treatment of enteritis with fluoroquinolones did not prevent the occurrence of ReA.

Taken together there is no evidence to date that antibiotic therapy is useful in acute and chronic reactive arthritis. This is especially true if the arthritis was triggered by an enteric infection. There is need for more

studies in patients with urogenital infections. Detection of *Chlamydia* in urethral or cervical swabs remains the only clear indication for antibiotic therapy including the sexual partner to prevent infertility. Such treatment is independent of the arthritis.

Connecting these results to the whole discussion about serology there are two main aspects: one is that there is no real need to do any serology in suspected reactive arthritis because the tests are not good enough and there are no clear therapeutical implications. The more positive aspect is that there are still things to be done.

References

1. Sieper J, Braun J. Pathogenesis of spondylarthropathies. Persistent bacterial antigen, autoimmunity, or both? *Arthritis Rheum* 1995;38:1547-54.
2. Sieper J, Kingsley G. Recent advances in the pathogenesis of reactive arthritis. *Immunol Today* 1996;17:160-3.
3. Wilkinson NZ, Kingsley GH, Sieper J, Braun J, Ward ME. Lack of correlation between the detection of *Chlamydia trachomatis* DNA in synovial fluid from patients with a range of rheumatic diseases and the presence of an antichlamydial immune response. *Arthritis Rheum* 1998;41:845-54.
4. Bas S, Griffais R, Kvien TK, Glennas A, Melby K, Vischer TL. Amplification of plasmid and chromosome *Chlamydia* DNA in synovial fluid of patients with reactive arthritis and undifferentiated seronegative oligoarthritis. *Arthritis Rheum* 1995;38:1005-13.
5. Gerard HC, Branigan PJ, Arayssi T, Klippel JH, Schumacher HR, Hudson AP. Viability of *Chlamydia pneumoniae* in synovial tissue of arthritis patients. *Arthritis Rheum* 1996;39: S183.
6. Braun J, Tuszewski M, Eggens U, Mertz A, Schauer-Petrowskaja C, Doring E, Laitko S, Distler A, Sieper J, Ehlers S. Nested polymerase chain reaction strategy simultaneously targeting DNA sequences of multiple bacterial species in inflammatory joint diseases. I. Screening of synovial fluid samples of patients with spondyloarthropathies and other arthritides. *J Rheumatol* 1997;24:1092-1100.
7. Gerard HC, Branigan PJ, Schumacher HR, Jr., Hudson AP. Synovial *Chlamydia trachomatis* in patients with reactive arthritis/Reiter's syndrome are viable but show aberrant gene expression. *J Rheumatol* 1998;25:734-42.
8. Nikkari S, Merilahti-Palo R, Saario R, Soderstrom KO, Granfors K, Skurnik M, Toivanen P. *Yersinia*-triggered reactive arthritis. Use of polymerase chain reaction and immunocytochemical staining in the detection of bacterial components from synovial specimens. *Arthritis Rheum* 1992;35:682-7.
9. Wilkinson N, Kingsley G, Jones H, Sieper J, Braun J, Ward M. The detection of DNA from a range of bacterial species in the joint of patients with a variety of arthritides using a nested, broad-range PCR. *Br J Rheumatol*, in press.
10. Nikkari S, Rantakokko K, Ekman P, Mottonen T, Leirisalo-Repo M, Virtala M, Lehtonen L, Jalava J, Kotilainen P, Granfors K, Toivanen P. *Salmonella*-triggered reactive arthritis: use of polymerase chain reaction, immunocytochemical staining, and gas chromatography-mass spectrometry in the detection of bacterial components from synovial fluid. *Arthritis Rheum* 1999;42:84-9.
11. Branigan PJ, Gerard HC, Hudson AP, Schumacher HR, Jr., Pando J. Comparison of synovial tissue and synovial fluid as the source of nucleic acids for detection of *Chlamydia trachomatis* by polymerase chain reaction [published errata appeared in *Arthritis Rheum* 1997 40:387 and 1997;40:782]. *Arthritis Rheum* 1996;39:1740-6.
12. Granfors K, Merilahti-Palo R, Luukkainen R, Mottonen T, Lahesmaa R, Probst P, Marker-Hermann E, Toivanen P. Persistence of *Yersinia* antigens in peripheral blood cells from patients with *Yersinia enterocolitica* O:3 infection with or without reactive arthritis. *Arthritis Rheum* 1998;41:855-62.
13. Toivanen A, Lahesmaa-Rantala R, Vuento R, Granfors K. Association of persisting IgA response with *Yersinia* triggered reactive arthritis: a study on 104 patients. *Ann Rheum Dis* 1987;46:898-901.

14. Kuipers JG, Jurgens-Saathoff B, Bialowons A, Wollenhaupt J, Kohler L, Zeidler H. Detection of Chlamydia trachomatis in peripheral blood leukocytes of reactive arthritis patients by polymerase chain reaction. *Arthritis Rheum* 1998;41:1894-5.
15. Wilbrink B, van der Heijden IM, Schouls LM, van Embden JD, Hazes JM, Breedveld FC, Tak PP. Detection of bacterial DNA in joint samples from patients with undifferentiated arthritis and reactive arthritis, using polymerase chain reaction with universal 16S ribosomal RNA primers. *Arthritis Rheum* 1998;41:535-43.
16. Yin Z, Braun J, Neure L, Wu P, Liu L, Eggens U, Sieper J. Crucial role of interleukin-10/interleukin-12 balance in the regulation of the type 2 T helper cytokine response in reactive arthritis. *Arthritis Rheum* 1997;40:1788-97.
17. Yin Z, Braun J, Neure L, Wu P, Eggens U, Krause A, Kamradt T, Sieper J. T cell cytokine pattern in the joints of patients with Lyme arthritis and its regulation by cytokines and anticytokines. *Arthritis Rheum* 1997;40:69-79.
18. Braun J, Yin Z, Krause A, Liu L, Spiller I, Sieper J. Peripheral blood cells of reactive arthritis patients secrete more IL-10 and less TNF- α than patients with Lyme- or rheumatoid arthritis. *Arthritis Rheum* 1997;40:S79.
19. Hohler T, Schaper T, Schneider PM, Meyer zum Buschenfelde KHM, Märker-Hermann E. Association of different tumor necrosis factor alpha promoter allele frequencies with ankylosing spondylitis in HLA-B27 positive individuals. *Arthritis Rheum* 1998;41:1489-92.
20. Deane KH, Jecock RM, Pearce JH, Gaston JS. Identification and characterization of a DR4-restricted T cell epitope within chlamydia heat shock protein 60. *Clin Exp Immunol* 1997;109:439-45.
21. Mertz AK, Ugrinovic S, Lauster R, Wu P, Grolms M, Botcher U, Appel H, Yin Z, Schiltz E, Batsford S, Schauer-Petrowski C, Braun J, Distler A, Sieper J. Characterization of the synovial T cell response to various recombinant Yersinia antigens in Yersinia enterocolitica-triggered reactive arthritis. Heat-shock protein 60 drives a major immune response. *Arthritis Rheum* 1998;41:315-26.
22. Ugrinovic S, Mertz A, Wu P, Braun J, Sieper J. A single non-amer from the Yersinia 60-kDa heat shock protein is the target of HLA-B27-restricted CTL response in Yersinia-induced reactive arthritis. *J Immunol* 1997;159:5715-23.
23. Mertz A, Wu P, Rudwaleit M, Braun J, Sieper J. Synovial T cell response to the heat shock protein 60 of Yersinia enterocolitica in Yersinia - arthritis patients: epitope analysis and cytokine secretion profile. *Arthritis Rheum* 1998;41:S131.
24. Zhou M, Sayad A, Simmons WA, Jones RC, Maika SD, Satumtira N, Dorris ML, Gaskell SJ, Bordoli RS, Sartor RB, Slaughter CA, Richardson JA, Hammer RE, Taurog JD. The specificity of peptides bound to human histocompatibility leukocyte antigen (HLA)-B27 influences the prevalence of arthritis in HLA-B27 transgenic rats. *J Exp Med* 1998;188:877-86.
25. Fendler C, Braun J, Eggens U, Laitko S, Sorensen H, Distler A, Sieper J. Bacteria-specific lymphocyte proliferation in peripheral blood in reactive arthritis and related diseases. *Br J Rheumatol* 1998;37:520-4.
26. Fendler C, Wu P, Eggens U, Laitko S, Sorensen H, Distler A, Braun J, Sieper J. Longitudinal investigation of bacterium-specific synovial lymphocyte proliferation in reactive arthritis and Lyme arthritis. *Br J Rheumatol* 1998;37:784-8.
27. Beacock-Sharp H, Young JL, Gaston JS. Analysis of T cell subsets present in the peripheral blood and synovial fluid of reactive arthritis patients. *Ann Rheum Dis* 1998;57:100-6.
28. Inman RD, Chiu B. Synovioocyte-packaged Chlamydia trachomatis induces a chronic aseptic arthritis. *J Clin Invest* 1998;102:1776-82.
29. Laitio P, Virtala M, Salmi M, Pelliniemi LJ, Yu DT, Granfors K. HLA-B27 modulates intracellular survival of Salmonella enteritidis in human monocyte cells. *Eur J Immunol* 1997;27:1331-8.
30. Ortiz-Alvarez O, Yu DT, Petty RE, Finlay BB. HLA-B27 does not affect invasion of arthritogenic bacteria into human cells. *J Rheumatol* 1998;25:1765-71.
31. Boyer GS, Templin DW, Bowler A, Lawrence RC, Everett DF, Heyse SP, Cornoni-Huntley J, Goring WP. A comparison of patients with spondyloarthropathy seen in specialty clinics with those identified in a communitywide epidemiologic study. Has the classic case misled us? *Arch Intern Med* 1997;157:2111-17.
32. Braun J, Bollow M, Remlinger G, Eggens U, Rudwaleit M, Distler A, Sieper J. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998;41:58-67.
33. Kvien T, Glennas A, Melby K, Granfors K, Andrup O, Karstensen B, Thoen J. Reactive Arthritis: Incidence, triggering agents and clinical presentation. *J Rheumatol* 1994;21:115-22.
34. Mattila L, Leirisalo-Repo M, Pelkonen P, Koskimies S, Granfors K, Siitonen A. Reactive arthritis following an outbreak of Salmonella Bovismorbificans infection. *J Infect* 1998;36:289-95.
35. Kingsley G, Sieper J. Third International Workshop on Reactive Arthritis. 23-26 September 1995, Berlin, Germany. Report and abstracts. *Ann Rheum Dis* 1996;55:564-84.
36. Pacheco-Tena C, Burgos-Vargas R, Vazquez-Mellado J, Cazarin J, Perez-Diaz JA. A proposal for the classification of patients to enter clinical and experimental studies on reactive arthritis. A study based on a review of inclusion criteria as appeared in scientific articles. *J Rheumatol* 1999; in press.
37. Sieper J, Braun J. Problems and advances in the diagnosis of reactive arthritis. *J Rheumatol* 1999; in press.
38. Wilkens RF. Reiter's syndrome: evaluation of preliminary criteria for definite disease. *Arthritis Rheum* 1981;24:844-9.
39. Amor B. Reiter's syndrome. *Rheum Dis Clin North Am* 24:677-695, 1998.
40. Calin A. Reactive arthritis. In: Calin A, Taurog J, eds. *Spondylarthropathies*. Oxford (UK): Oxford University Press, 1998.
41. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, Cats A, Dijkman B, Olivieri I, Pasero G. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34:1218-27.
42. Sieper J, Braun J. Treatment of reactive arthritis with antibiotics [editorial]. *Br J Rheumatol* 1998;37:717-20.
43. Maki-Ikola O, Heesemann J, Toivanen A, Granfors K. High frequency of Yersinia antibodies in healthy populations in Finland and Germany. *Rheumatol Int* 1997;16:227-9.
44. Maki-Ikola O, Lahesmaa R, Heesemann J, Merilahti-Palo R, Saario R, Toivanen A, Granfors K. Yersinia-specific antibodies in serum and synovial fluid in patients with Yersinia triggered reactive arthritis. *Ann Rheum Dis* 1994;53:535-9.
45. Maki-Ikola O, Arvilommi H, Gaston JS, Granfors K. Salmonella antibodies in healthy populations in Finland and the UK - how many Salmonella-triggered reactive arthritides are there? [letter]. *Br J Rheumatol* 1993;32:262-3.
46. Maki-Ikola O, Leirisalo-Repo M, Kantele A, Toivanen P, Granfors K. Salmonella-specific antibodies in reactive arthritis. *J Infect Dis* 1991;164:1141-8.
47. Sieper J, Braun J, Reichardt M, Eggens U. The value of specific antibody detection and culture in the diagnosis of reactive arthritis. *Clin Rheumatol* 1993;12:245-52.
48. Bas S, Vischer TL. Chlamydia trachomatis antibody detection and diagnosis of reactive arthritis. *Br J Rheumatol* 1998;37:1054-9.
49. Bas S, Cunningham T, Kvien TK, Glennas A, Melby K, Vischer TL. The value of isotype determination of serum antibodies against Chlamydia for the diagnosis of Chlamydia reactive arthritis. *Br J Rheumatol* 1996;35:542-7.
50. Bas S, Cunningham T, Kvien TK, Glennas A, Melby K, Vischer TL. Synovial fluid and serum antibodies against Chlamydia in different forms of arthritis: intra-articular IgA production in Chlamydia sexually acquired reactive arthritis. *Br J Rheumatol* 1996;35:548-52.
51. Gaydos CA, Howell MR, Pare B, Clark KL, Ellis DA, Hendrix RM et al. Chlamydia trachomatis infections in female military recruits. *N Engl J Med* 1998;339:739-44.
52. Sieper J, Fendler C, Laitko S, Sorensen H, Gripenberg-Lerche C, Hiepe F, Alten R, Keitel W, Groh A, Uksila J, Eggens U, Granfors K, Braun J. No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis. *Arthritis Rheum* 1999; in press.
53. Lauhio A, Leirisalo-Repo M, Lahdevirta J, Saikku P, Repo H. Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special reference to Chlamydia arthritis. *Arthritis Rheum* 1991;34:6-14.
54. Wollenhaupt J, Hammer M, Pott HG, Zeidler H. A double-blind, placebo-controlled comparison of 2 weeks versus 4 months treatment with Doxycycline in Chlamydia-induced reactive arthritis. *Arthritis Rheum* 1997;40:S143.
55. Bardin T, Enel C, Cornelis F, Salski C, Jorgensen C, Ward R, Lathrop GM. Antibiotic treatment of venereal disease and Reiter's syndrome in a Greenland population. *Arthritis Rheum* 1992;35:190-4.
56. Loch H, Kihlstrom E, Lindstrom FD. Reactive arthritis after Salmonella among medical doctors - study of an outbreak. *J Rheumatol* 1993;20:845-8.