Treating reactive arthritis: insights for the clinician

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Abstract: There are two main forms of reactive arthritis (ReA): postvenereal and postdysentery. *Chlamydia trachomatis* (Ct) is the major causative organism of the postvenereal type; *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* are the major triggers for the postenteric type. All of these causative organisms have been shown to traffic to the synovium in affected individuals. However, one important difference is that the chlamydial organisms have been shown to be viable, whereas, in general, the postenteric organisms are not. Although estimates vary widely, it is felt that 30–50% of all cases of ReA become chronic and the remainder resolve spontaneously within weeks to months. These important differences need to be considered when reviewing the available therapeutic outcomes data. There is a relative paucity of prospective clinical trial data assessing various treatment strategies. A large breadth of clinical experience demonstrates that nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are efficacious, but there have only been two rather small trials assessing NSAIDs and none with corticosteroids. Disease modifying drugs are sometimes utilized in more severe or chronic cases, but only sulfasalazine (SSZ) has been studied. Anti-tumor necrosis factor (TNF) therapy has proved remarkably efficacious with other types of spondyloarthritides, but there is very little data to support their use in ReA; theoretical concerns also exist with this drug class in ReA, specifically. Finally, antibiotics have been studied in several trials. A thorough analysis of these trials reveals equivocal results with a possible particular benefit in postchlamydial ReA. These data are reviewed with an emphasis on postchlamydial and postenteric ReA.

Keywords: reactive arthritis, spondyloarthritis, Reiter's syndrome, drug therapy

Introduction

Tremendous insight has been gained into the pathogenesis of reactive arthritis (ReA). In general, there are two main types of ReA: postvenereal and postenteric. *Chlamydia trachomatis* (Ct), *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* are all known triggers for this condition [Carter, 2006]. However, several other organisms have been implicated as potential, yet less common, causes. These include *Chlamydophila* (*Chlamydia*) *pneumoniae* [Hannu *et al.* 1999; Braun *et al.* 1994], *Ureaplasma urealyticum* [Horowitz *et al.* 1994], *Escherichia coli* [Townes *et al.* 2008], *Clostridium difficile* [Birnbbaum *et al.* 2008], intravesicular *Bacillus Calmette-Guerin* (BCG) [Tinazzi *et al.* 2006], *Helicobacter pylori* [Melby *et al.* 1999], and various intestinal parasites. Because the vast majority of cases of ReA are caused by the venereal and enteric organisms listed initially and due to

the fact the causative role of some of the other organisms cited is speculative, this review article will focus on the treatment of ReA in general with a special emphasis on the two main disease types; i.e. the postvenereal and postenteric type.

ReA represents the prototypical interplay of host and environment. The classic syndrome is a triad of symptoms including the urethra, conjunctiva, and synovium; however, the majority of patients do not present with this classic triad [Carter, 2006]. These symptoms typically start within 1–6 weeks after the inciting infection. Many cases of ReA resolve spontaneously weeks to months after the onset of symptoms, yet the condition can become chronic (i.e. lasting longer than 6 months) in approximately 30–50% of patients [Carter and Hudson, 2009]. In those

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who experience chronic disease, the symptoms can exhibit a remitting pattern.

Denys Ford, M.D., a modern pioneer in the field of ReA, has unraveled many of the mysteries that surround this and several other rheumatic conditions. Ford previously formulated the hypothesis that one agent may cause different clinical syndromes and one syndrome may be due to many infectious agents [Ford, 1987]. Perhaps there is no better example in medicine to support this theory than ReA. Mysteriously, the causative organisms that are responsible for ReA trigger the disease in only a minority of patients who experience an acute genitourinary or gastrointestinal infection. Even more cryptic is the fact that one organism, for example Ct, can cause a complete triad of symptoms in one patient, an incomplete form in another, chronic disease in some, while the symptoms abate spontaneously in others. Such enigmatic sequelae from a single infecting organism can prove problematic when it comes to the therapeutic management of this condition. It also suggests that although we have learned much about disease initiation in ReA, disease maintenance, and therefore potential therapy, remains a conundrum.

Data suggest that ReA is underdiagnosed or often misdiagnosed. A review of the data with postchlamydial ReA is illustrative. Well-established epidemiological data demonstrate that approximately 4% of patients who develop an acute Ct infection will develop ReA [Rich *et al.* 1996]. The Centers for Disease Control monitor all Ct infections in the US on a yearly basis. These data demonstrate that there are approximately 3,000,000 new Ct infections in the US every year among people 15–44 years of age [Groseclose *et al.* 1999]. Taken together, there should be approximately 120,000 new cases of Ct-induced ReA every year in the US. As a comparison, the estimated annual incidence of rheumatoid arthritis in the US is 44.6/100,000 [Doran *et al.* 2002]. With an estimated US population of 300 million people, this would equate to 133,000 new cases of rheumatoid arthritis per year in the US. Thus, the incidence of Ct-induced ReA in the US should rival the incidence of rheumatoid arthritis. This estimated incidence of ReA is also low because it does not include the other causative organisms. Thus, incident cases of ReA in the US should far outnumber the incident cases of rheumatoid arthritis. This clearly is not the case. Several published studies suggest that the

spondyloarthritides, in general, affect about 1% of the population and doctor-diagnosed ReA encompasses only a small fraction of the spondyloarthritides [Olivieri *et al.* 2002]. A vast breadth of clinical experience also tells us that rheumatoid arthritis is a much more common diagnosis than ReA. The reasons for this are not entirely clear. However, a partial explanation might lie in the fact that many cases of ReA resolve spontaneously. An over-reliance on the complete clinical triad and/or the presence of human leukocyte antigen (HLA)-B27 might also account for underdiagnosis [Carter and Hudson, 2009]. Finally, recent data suggest that asymptomatic initial chlamydial infections can also lead to cases of ReA thereby making the triggering infection less clinically apparent [Carter *et al.* 2009]. Regardless, these data suggest that clinicians need to be more alert to ReA in order to properly diagnose their patients.

A final introductory point for this review involves the terminology for the condition itself. The literature can be quite confusing in this regard. Throughout the years, ReA has been labeled with several different eponyms, most notably Reiter's syndrome. During World War II, Hans Reiter authorized medical experiments on concentration camp prisoners. Because of this, some have correctly argued against the use of the Reiter eponym [Panush *et al.* 2007]. In recent years, use of the term 'Reiter syndrome' has been in decline [Lu and Katz, 2005] and the term 'reactive arthritis' has been utilized. In some instances, the term 'Reiter syndrome' has been reserved for subjects who exhibit the complete triad of symptoms. However, we now know that most subjects do not exhibit clinical manifestations in all three organ systems; patients might also develop symptoms in end organs that are not part of the 'classic' triad (e.g. skin: keratoderma blenorrhagicum or circinate balanitis). Further, the term 'reactive arthritis' is a more descriptive term. For these reasons, the term 'Reiter's syndrome' should be abandoned and the appropriate terminology for this condition is 'reactive arthritis' regardless of whether the patient's symptoms involve the three classic organ systems.

Pathogenesis of reactive arthritis

In order to better understand the appropriate therapeutic management of ReA, a brief review of the pathogenesis of ReA is warranted. As stated, there are vast data implicating several different bacterial infections as triggers for ReA.

The most accepted include *Ct*, *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*. Of all the bacterial causes of ReA, *Ct* is the most common [Barth and Segal, 1999]. However, the four enteric organisms listed cause more cases of ReA as a group than postchlamydial ReA.

For years it was apparent that these causative organisms had the capability of triggering ReA; yet there was a disconnect. Patients would experience an acute venereal or enteric infection and in the ensuing weeks develop an inflammatory arthritis with other potential extra-articular manifestations. Investigations were performed on these patients to demonstrate the presence of these causative organisms in the synovial fluid of these ReA patients. However, cultures were routinely sterile. It was questioned whether these organisms made it to the synovium at all; the thought was these triggering organisms would initiate an autoimmune response that resulted in ReA, possibly via the HLA-B27. It has been postulated that HLA-B27 presents arthritogenic microbial peptides to T-cells stimulating an autoimmune response; so-called molecular mimicry. A previous study has shown a high degree of conservation in the T-cell responses obtained from the synovial fluid of patients with recent ReA irrespective of the triggering organism [Dulphy *et al.* 1999]. However, only 30–50% of ReA patients are HLA-B27 positive and recent data suggest this haplotype might predispose more to disease severity rather than disease susceptibility [Carter and Hudson, 2009].

While the debate regarding autoimmune response *versus* disseminated 'infection' continues, the advent of polymerase chain reaction (PCR) analysis has added much insight and clarity into the pathophysiology of ReA. Many published studies in several different laboratories have demonstrated the presence of all the causative organisms in the synovial fluid and/or tissue of these ReA patients [Nikkari *et al.* 1999; Gerard *et al.* 1998; Braun *et al.* 1997; Granfors *et al.* 1992]. There is little doubt that these causative organisms traffic from the initial site of infection (i.e. the gastrointestinal or genitourinary tract) to the synovium and possibly other involved tissues [Carter *et al.* 2008]. The question remains, however, whether these positive PCR findings indicate that these ReA patients experience a disseminated persistent infection that is the driving force of their ReA or if the disseminated presence of these causative organisms simply lays the

foundation for an autoimmune phenomenon through a mechanism that is not completely understood.

As remarkable as it might be that all of the causative organisms traffic from the initial site of infection to the synovium, there are surprising differences between the postvenereal and postenteric organisms once they reside in that end-organ. Studies from many laboratories have demonstrated that *Ct*, like *Mycobacterium tuberculosis*, can undergo long-term, persistent infections [Gerard *et al.* 2002]. As stated, the routine presence of *Ct* has been demonstrated by PCR in the synovial tissue of patients with ReA [Gerard *et al.* 1999]. Of special interest is the fact that these chlamydiae are viable, albeit in an aberrant state. The pattern of gene expression is significantly different in the persistent infection state *versus* that seen during normal active infection. For example, during persistence, expression of the major outer membrane protein (*omp1*) gene and several genes required for the cell division process are severely downregulated. This is coupled with differential regulation of the three paralog genes specifying the *Ct* HSP-60 proteins (*Ct110*, *Ct604*, and *Ct755*) [Gerard *et al.* 2004]. In addition, the chlamydial life cycle in the persistent state is attenuated. These persistently-infecting, viable chlamydiae have been demonstrated years after the initial infection. Similar PCR studies have demonstrated *C. pneumoniae* in the synovial tissue of patients with ReA, although it is less commonly detected [Gerard *et al.* 2000]. As stated, PCR technology has also demonstrated the presence of chromosomal DNA from the known triggers in the synovial tissue of patients with the postdysentery form of ReA. Unlike persistently viable chlamydiae, the synovial-based postenteric organisms have not been shown to be viable, with the possible exception of *Yersinia* [Gaston *et al.* 1999]. While this very important difference between the postvenereal and postenteric forms of ReA leads to more questions such as how these two different findings could lead to the same clinical endpoint, it could also have very important therapeutic consequences.

Therapy of reactive arthritis

In keeping with the notion that ReA might be underdiagnosed, there are a limited number of prospective randomized trials assessing different therapeutic modalities as a treatment for ReA. Paralleling the opposing schools of thought

regarding the pathophysiology of the disease, both traditional disease modifying antirheumatic drugs (DMARDs) and antibiotics have been assessed as potential therapeutic options. However, there are far more data with antibiotics. In almost ironic fashion, the quizzical differences between the persistently viable synovial-based chlamydiae and the apparent non-viable post-enteric synovial based organisms; the data regarding the efficacy of antibiotics is generally felt to be negative with some notable exceptions. Recent data also increase hope with this treatment approach. These and other treatment options will be reviewed.

Nonsteroidal anti-inflammatory drugs

Although a very large breadth of clinical experience tells us that NSAIDs are effective as a treatment for ReA, there are only two rather small prospective trials that have formally evaluated their use for this condition. The first was a double-blind crossover study comparing azapropazone (available in the United Kingdom) to indomethacin [Lassus, 1976]. This study analyzed 1200 mg of azapropazone daily *versus* 100 mg of indomethacin daily in patients with both psoriatic arthritis and ReA. Although this study only included 16 patients with ReA, it did suggest that indomethacin might be more effective as a treatment for ReA than azapropazone; however, there were also more side effects with indomethacin. Neither medication helped with the skin manifestations of either condition.

The second study analyzing the efficacy of NSAIDs in ReA was another double-blind crossover study comparing ketoprofen to indomethacin [Juvakoski and Lassus, 1982]. In this study of 50 subjects with ReA both ketoprofen and indomethacin were efficacious at treating articular symptoms of ReA, but there was no significant difference between the two NSAIDs studied. Similar to the other NSAID study, there were more side effects with indomethacin.

Rather intriguing evidence exists suggesting that the NSAIDs might have a disease modifying effect on other types of spondyloarthritides, most notably ankylosing spondylitis [Wanders *et al.* 2005]. Although ReA is not believed to cause as pronounced pathologic bony sequelae as ankylosing spondylitis, there are no data to show if NSAIDs might have a similar disease modifying effect in ReA. There are also no studies to suggest that these drugs might accelerate

remission or have any effect on any of the extra-articular features of this condition.

Corticosteroids

Similar to NSAIDs, there are very few data formerly evaluating the use of corticosteroids in ReA. Yet a long history of clinical use suggests they are beneficial. It has been suggested that the use of systemic corticosteroids might be more efficacious in the treatment of peripheral articular symptoms rather than the axial symptoms [Flores *et al.* 2003]. Because ReA often involves large joints (e.g. knee), intra-articular corticosteroids are often a useful treatment strategy, particularly in early ReA. It also appears that corticosteroids are a useful treatment for many of the extra-articular features of ReA including iritis/uveitis, keratoderma blenorrhagicum, and circinate balanitis; topical corticosteroids preparations might be particularly useful for these features of ReA with the obvious benefit of less potential side effects [Flores *et al.* 2003].

Because bacterial persistence is a hallmark feature of ReA and in the case of postchlamydial ReA the triggering organisms remain viable in the synovium, potentially years after the initial exposure, theoretical concerns could exist. This might be particularly relevant in early ReA. However, there are no longitudinal data in ReA to assess if the use of corticosteroids might predispose to chronic disease.

Disease modifying antirheumatic drugs

As stated, ReA has the capability of progressing to chronic disease. It also can cause joint damage if left untreated. In many respects, the potential radiographic sequelae mirror those of psoriatic arthritis. For these reasons, DMARDs are often utilized in patients with ReA, particularly those with chronic disease or more severe symptoms. The best studied DMARD in the setting ReA is sulfasalazine (SSZ). A prospective, placebo-controlled trial assessing SSZ at a dose of 2000 mg/day was assessed in 134 subjects (69 subjects on SSZ and 65 on placebo) with chronic ReA in a Department of Veterans Affairs Cooperative Study [Clegg *et al.* 1996]. The projected sample size of 240 subjects was not achieved. All subjects had failed to respond to NSAIDs and were followed in the study for 36 weeks. The subjects' mean duration of disease was ~10 years. The definition of response was based on joint tenderness and swelling scores as

well as patient and physician global assessments. Using the last observation carried forward technique, the response rates were 62.3% in the SSZ group and 47.7% in the placebo group ($p=0.089$). An analysis of secondary outcome measures resulted in significant improvement in some endpoints in the SSZ treated subjects including the Spondylitis Articular Index ($p=0.05$) and the Westergren Erythrocyte Sedimentation Rate (ESR) ($p=0.002$). However, the C-reactive protein values were not significantly different in the SSZ *versus* the placebo group. A longitudinal analysis did reveal improvement in the subjects taking SSZ compared to placebo ($p=0.02$). Although the inclusion criteria were rather stringent requiring several features consistent with ReA, there was no effort to determine the initial triggering infection to determine if certain types of ReA might have fared better (e.g. postenteric ReA). The primary adverse events in subjects on SSZ were gastrointestinal in nature.

SSZ was analyzed in another double-blind, placebo-controlled study of 6 months duration [Egsmose *et al.* 1997]. In this trial, SSZ was tested in 79 subjects (37 on SSZ and 42 on placebo) at a dose of 2–3 g/day. An important difference with this trial compared to the previously mentioned SSZ trial was that the study subjects in this trial had acute ReA with mean disease duration of 4.7 months in the SSZ group and 3.9 months in the placebo group. Intention-to-treat analysis revealed no significant difference between the two groups in terms of pain, number of swollen joints and ESR. Because this was a study analyzing treatment effect in patients with acute ReA, and acute ReA often remits spontaneously, significant improvement was noted in both the SSZ and placebo-treated patients. However, the number of days on sick leave improved significantly in the SSZ group ($p < 0.01$) but not the placebo group. Complete remission was achieved in significantly more SSZ-treated patients at month 2, but there was no difference between the groups at month 6. There was no apparent efficacy difference in patients regarding the initial triggering infection, HLA-B27 status, or presence/absence of axial arthritis. However, the study was not properly powered to fully assess these secondary endpoints. Gastrointestinal adverse events were more prominent in the SSZ treat group and in total 23 (29%) of the subjects withdrew

prematurely (15 in the SSZ group and eight in the placebo group).

SSZ has been employed for years as a treatment for inflammatory bowel disease. Interestingly, in a histopathology study of 55 subjects with ReA it was demonstrated that 67% had histologic evidence consistent with inflammatory bowel disease on bowel biopsies, even in the absence of gastrointestinal symptoms [Cuvelier *et al.* 1987]. Of these ReA subjects, it was felt that 46 (84%) had the postenteric variety. These histopathologic findings might suggest that SSZ would be a good choice for chronic postenteric ReA. However, we do not have clinical trial data that has focused on postenteric ReA patients to confirm this possibility.

Therefore, the data suggest that SSZ might be moderately effective as a treatment for chronic ReA, but it appears to offer little benefit in the setting of acute ReA. Somewhat surprisingly, there are no prospective trials analyzing other DMARDs in the setting of ReA. Methotrexate, azathioprine, and cyclosporine have been advocated as potential treatments for ReA but never formally evaluated.

Tumor necrosis factor-alpha antagonists

The tumor necrosis factor (TNF) -alpha antagonists have demonstrated remarkable success in treating several types of inflammatory arthritis including other types of spondyloarthritides, namely ankylosing spondylitis and psoriatic arthritis. Therefore it might seem logical that they would be useful therapeutic agents for ReA. Indeed, patients with ReA exhibit higher serum levels of TNF-alpha levels compared to normal controls [Rihl *et al.* 2004]. This suggests potential benefit from TNF-alpha antagonists. However, there are conflicting data regarding the role of Th1 and Th2 cytokines in ReA; there are also theoretical concerns regarding TNF-alpha antagonism in ReA. Although ReA patients have higher serum TNF-alpha than normal controls, lower levels of TNF-alpha have been demonstrated in ReA compared to other types of inflammatory arthritis. Several studies suggest ReA is more of a Th2 driven disease [Thiel *et al.* 2000; Braun *et al.* 1999; Yin *et al.* 1997], yet another suggests the Th1 *versus* Th2 predominance depends on the cell analyzed (synovial fluid derived T-cell clones *versus* synovial fluid mononuclear cells) [Rihl *et al.* 2004]. Further, the trigger of ReA is known to be an

acute bacterial infection and bacterial persistence with the causative organisms has been demonstrated in the synovial tissue. In the case of chlamydiae, specifically, these persistent bacterial organisms remain viable. Adding to these concerns, *in vitro* data has demonstrated that persistent chlamydial levels are inversely proportional to TNF-alpha levels [Ishihara *et al.* 2005; Takano *et al.* 2005; Perry *et al.* 1997]. In keeping with the relative lack of prospective clinical trial data with ReA in general, there are few prospective data evaluating anti-TNF therapy in ReA.

There are no randomized trials in ReA to accurately assess the efficacy of anti-TNF therapy. Several case reports and a small open-label study suggest clinical benefit with these drugs in the treatment of ReA [Schafranski, 2009; Flagg *et al.* 2005; Haibel *et al.* 2003; Oili *et al.* 2003]. The largest amount of data available is from the small open-label study assessing etanercept in 16 patients with undifferentiated or ReA [Flagg *et al.* 2005]. Ten of the 16 patients completed the 6-month study. Nine of the 10 completers were considered responders; however, one of these patients required a total knee replacement 6 months after beginning therapy. The other cases reports include three cases of postenteric ReA and one case of presumed postchlamydial ReA; all four subjects reported improvement with infliximab.

Interestingly, the small open-label trial of 16 patients did include synovial biopsies to assess for chlamydiae by PCR before and after treatment with etanercept. There were three patients who were PCR positive for chlamydiae in the synovium before treatment. Of these three, two became PCR negative on therapy and one remained PCR positive. However, two patients with negative PCR results at baseline became PCR positive for chlamydiae while on etanercept. In another preliminary experiment, the relative bacterial load in paired synovial tissue samples from a patient with Ct-induced ReA was assessed before and after several months of treatment with etanercept. Real time PCR analyses demonstrated that the second biopsy sample held a bacterial load that was several-fold higher than that of the initial, pretreatment sample [personal communication with Alan P. Hudson, PhD., November 2008]. Interestingly, this same patient experienced clinical improvement in spite of the increased bacterial synovial load while on therapy. Finally, a case series of three patients with

rheumatoid arthritis who developed a new palmoplantar-pustular rash while on anti-TNF therapy were all found to be PCR positive for Ct on skin biopsies of the affected areas [Carter *et al.* 2008]. Taken together, these PCR data in patients on anti-TNF therapy lend possible credence to the theoretical concerns.

The limited clinical data we have regarding the TNF-alpha antagonists in ReA suggest possible therapeutic benefit. However, there also exists a small amount of accompanying PCR data, specifically with *Chlamydia*, that raises possible concern. Because of these somewhat conflicting data, the TNF-alpha antagonists should only be used in the most refractory ReA cases; it might also be prudent to restrict their use to postenteric ReA until we learn more.

Antibiotics

We have known for many years that certain bacterial organisms are responsible for the genesis of ReA. This makes the notion of using antibiotics as treatment intriguing. Many trials that have assessed the utility of several different antibiotics have been performed. More recent data have demonstrated that the causative bacterial organisms traffic from the initial site of infection to the synovium, thus making this potential treatment approach more plausible. Important advances in our understanding the role these organisms play in the synovial-based pathophysiology have taught us that in the case of persistent synovial-based chlamydiae, specifically, these organisms exist in a viable, albeit aberrant, state. This important apparent difference in the pathophysiology of postchlamydial *versus* postenteric ReA suggests these two clinically indistinct entities might need to be considered in terms of therapeutic approach; what do the data tell us regarding the efficacy of antibiotics in ReA?

The first well-designed prospective trial assessing antibiotics as a therapeutic option offered hope [Lauhio *et al.* 1991]. In this trial, patients with both postchlamydial and postenteric ReA were treated with either lymecycline or placebo in a double-blind fashion for 3 months. Interestingly, lymecycline significantly decreased the duration of illness in those subjects with postchlamydial ReA, but not those with the postenteric variety. These seemingly conflicting results led to a healthy debate that continues to this day. Critics cited data that later demonstrated that tetracycline antibiotics possess anti-inflammatory

properties, thereby lending a potential explanation for the benefit [Sadowski and Steinmeyer, 2001]. However, if the explanation for the improvement observed in this trial was truly the anti-inflammatory effect of the drug, then it would seem logical that both postchlamydial and postenteric subjects should have fared equally. This was not the case.

This initial study that seemed to support the use of prolonged antibiotics as a treatment for ReA led to several studies assessing various antibiotics in the ensuing years [Kvien *et al.* 2004; Smieja *et al.* 2001; Yli-Kerttula *et al.* 2000; Sieper *et al.* 1999; Wakefield *et al.* 1999]. The initial concept that postvenereal and postenteric ReA might behave differently in terms of therapeutic response, however, was somewhat lost in these follow-up studies. Further, the disease state was expanded to include patients with anterior uveitis as their only disease manifestation in one study [Wakefield *et al.* 1999]. These somewhat more ambitious studies assessing ciprofloxacin, azithromycin, and doxycycline produced negative results. The hope provided by the earlier study was dashed and the consensus was that prolonged antibiotics had no effect on the disease manifestations of ReA.

A more thorough look at these 'negative' clinical trial data, however, reveals a flicker of hope. A subgroup analysis of one of these trials that analyzed ciprofloxacin as a potential therapeutic agent suggested benefit in those patients with postchlamydial ReA, specifically [Sieper *et al.* 1999]. A follow-up of one of the 'negative' ciprofloxacin trials suggested that this antibiotics significantly improved the long-term prognosis when compared to those patients treated with placebo [Yli-Kerttula *et al.* 2003]. While these findings are of interest, the other negative trials did also enroll patients with presumed *Chlamydia*-induced ReA and with no apparent benefit.

By evaluating the data in such a manner, the results appear more equivocal than truly negative. It is apparent, however, that any potential benefit is more applicable to the postchlamydial patients. There are no data suggesting that prolonged antibiotic treatment is efficacious in patients with postenteric ReA. This mirrors the synovial-based pathophysiology findings. Could there be other explanations for these apparent equivocal results even in postchlamydial ReA patients? The minimum inhibitory concentration

of a given antibiotic is well-known in the treatment of acute chlamydial infections. However, individuals with Ct-induced ReA harbor persistent organisms with an attenuated life-cycle, thus raising questions about the validity of the standard means of testing for drug efficacy. Further, the accessibility of these drugs into the synovium after standard oral administration is largely unknown. Perhaps most important, *in vitro* data has demonstrated that standard concentrations of many different antibiotics, including ciprofloxacin, azithromycin, and doxycycline, when used as a potential treatment for persistent chlamydial infections, further induce the persistent state rather than clearing the infection [Dreses-Werringloer *et al.* 2000]. These same *in vitro* studies have further demonstrated that when a combination of azithromycin and rifampin are utilized as a treatment for persistent chlamydiae, the persistent chlamydial infection is eradicated [Dreses-Werringloer *et al.* 2001].

Taken together, these data suggest that combination antibiotics might be an efficacious therapeutic approach in patients with postchlamydial ReA. Other *in vitro* data suggest that rifampin might be a necessary component of any combined antimicrobial approach. The hallmark feature of persistent chlamydial infections is persistent upregulation of chlamydial heat shock proteins with downregulation of the other proteins that are characteristic of an acute chlamydial infection [Gerard *et al.* 2002]. Rifampin has been shown to attenuate chlamydial production of heat shock proteins [Engel *et al.* 1990]. A clinical trial assessed a 9-month course of a combination of doxycycline and rifampin *versus* doxycycline monotherapy in patients with suspected Ct-induced ReA [Carter *et al.* 2004]. Those subjects who received combination antibiotics demonstrated statistically significant improvement compared to those who received doxycycline monotherapy; however, there was no placebo control. Studies are ongoing to assess the efficacy of combination antimicrobial therapy in Ct-induced ReA.

Conclusion

Our insight into the disease initiation of ReA distinguishes this type of inflammatory arthritis from several others. Many recent advances have taught us about the pathophysiology of this condition. However, as the famous proverb suggests, "The more you know, the less you understand".

The best therapeutic approach for ReA is still shrouded in mystery.

It seems clear, however, that Dr Denys Ford was exactly correct with his hypothesis that one agent may cause different clinical syndromes and one syndrome may be due to many infectious agents. Regardless of whether combination antibiotics will prove to be a definitive treatment for post-chlamydial ReA or whether anti-TNF therapy is the most efficacious form of therapy for chronic postenteric ReA, the data suggest enough difference in the therapeutic response between the two major variants of ReA that all future clinical trials should be cognizant of this heterogeneity. The practice of taking clinically indistinct endpoints and analyzing treatment effect based on its bacterial genesis might allow us to unravel the therapeutic complexity that surrounds ReA.

Conflict of interest statement

None declared.

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