Chlamydia-induced reactive arthritis: the potential for eradication

"*Combination antimicrobial therapy as a potential cure for persistent chlamydial infections would not only transform the treatment of* Chlamydia*-induced ReA, it could have important implications in many chronic diseases.*"

KEYWORDS: ***Chlamydia pneumoniae*** ▪ ***Chlamydia trachomatis*** ▪ **drug therapy** ▪ **reactive arthritis**

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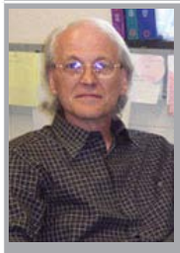

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The human genome project, gene therapy and nanotechnology are just a few of the remarkable advances in modern medicine. As medical science evolves, the potential cure of human disease seems more attainable. In apparent juxtaposition to these focused therapeutic strategies that aim at treating human disease at the genetic level, remains the seemingly archaic paradigm that bacterial or viral agents might also be causative of chronic human diseases. Certainly, these environmental triggers have the ability to alter the genetic makeup of an individual, leading to mutations that could cause disease in that same individual or even lead to major genetic shifts in the population at large. However, can persistent infections, either bacterial or viral, be etiologic of chronic human disease? The literature is replete with controversy involving many environmental agents including Epstein–Barr virus and *Borrelia burgdorferi*. Do these agents trigger a genetic response in susceptible individuals and then have no further role in disease maintenance, or are some responsible for both the genesis and propagation of disease? If the latter is true, can eradication of the persistent organism ameliorate, or even cure, the disease process? The evolving story of *Chlamydia*-induced reactive arthritis (ReA) offers many insights into these important questions.

Beginning with the demonstration in the late 1980s and early 1990s that *Helicobacter pylori* is an etiologic agent for certain ulcers [1], the notion that bacterial, viral and possibly fungal pathogens can play either an initiating or exacerbatory role in chronic disease has gained increasing credence [2–5]. In the case of *Chlamydia trachomatis,* it has long been recognized that the sequelae of primary genital infection can be severe; those sequelae include not only chronic ReA [6–8], but also temporomandibular joint dysfunction [9] and, in women, fertility deficit [10] and possibly cervical cancer [11]. *Chlamydia pneumoniae* has been linked to asthma, chronic obstructive pulmonary disease [12], atherosclerosis [13–15], neurologic diseases, including multiple sclerosis [16,17] and temporal arteritis [18], among other clinical entities; many of these latter associations remain controversial. However, much evidence supports a role for *C. pneumoniae* in the genesis of ReA [19,20], although this is a much less common cause of ReA than *C. trachomatis.*

When *C. trachomatis* and *C. pneumoniae* disseminate from their sites of primary infection, they can take up long-term residence at distant anatomic locations [21]; in the case of *Chlamydia*-induced ReA, these organisms traffic to the synovial tissue [20,22]. At those sites, both usually enter an unusual biological state referred to as 'persistence' [23]. In this state, a block in gene expression precludes completion of the developmental cycle, and the organisms display unusual morphological, transcriptional, and other properties [24]. In addition to the transcription system, the chlamydial protein synthetic system behaves differently during persistent infection [25]. 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 *C. trachomatis* (Ct) heat shock protein (HSP)-60 proteins (Ct110, Ct604 and Ct755) [26]. *In vivo,* synovial cells that are infected with persistent Ct display moderate upregulation of Ct110, significant upregulation of Ct604 and downregulation of Ct755. The principal host cell *in vivo* for persistent synovial Ct is the macrophage. Further, there is differential expression of these HSP-60 paralogs when comparing *in vitro* and *in vivo* samples in persistent infections [26]. Ct110 is downregulated *in vitro* in infected monocytes, but it remains

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persistently elevated *in vivo* in synovial cells. Ct604 is significantly upregulated both *in vitro* and *in vivo.* Lastly, Ct755 transcription is downregulated both *in vitro* and *in vivo* in persistently infected cells. The means by which persistently infecting chlamydiae engender pathology is poorly understood, although it is clear that they do elicit a strong immunopathogenic response.

Certain bacterial infections have unequivocally been demonstrated to be causative of ReA in a percentage of individuals who are exposed to these organisms. These organisms include chlamydiae as well as some enteric pathogens, namely *Salmonella, Shigella, Campylobacter* and *Yersinia.* Remarkably, the phenotypic expression of ReA is the congruent whether the trigger is chlamydiae or one of these enteric pathogens. However, important differences in the pathophysiology exist. One important difference in postchlamydial ReA versus postdysentery ReA is that these chlamydiae can exist in a persistent metabolically active state, whereas the postenteric organisms do not, with the possible exception of *Yersinia* [27]. The fact that these chlamydiae exist in a persistently viable state suggests they might be susceptible to antimicrobial therapy.

> *"...can persistent infections, either bacterial or viral, be etiologic of chronic human disease? The literature is replete with controversy..."*

The current standard-of-care therapy for patients with chronic ReA is adapted from the treatment strategies of other chronic inflammatory arthritidies, such as rheumatoid arthritis. These treatment strategies include various disease-modifying antirheumatic drugs such as sulfasalazine and methotrexate. There is a surprising lack of data regarding the efficacy and safety of disease-modifying antirheumatic drugs in the treatment of chronic ReA. Indeed, previous studies have suggested only modest improvement with sulfasalazine [28] and there are no prospective data analyzing methotrexate. Some recent reports have suggested that anti-TNF therapy might be an effective treatment for chronic ReA, but these reports are few and primarily involve postdysentery ReA [29–31]. The rationale for the use of traditional disease-modifying antirheumatic drugs or biologics aims at suppressing the chronic inflammation associated with this condition. Can we do better? Should our goal be successful inhibition of the ongoing inflammatory response or should we strive to eliminate the very source of inflammation itself? Is this even possible?

As stated, upregulation of chlamydial HSP-60 is the hallmark feature of synovial-based chlamydiae. HSPs are thought to serve many purposes, one of which is to confer antibiotic resistance [32]. Therefore, abrogation of this gene protein might be essential if eradication of the infected cell is to occur. Rifampin targets RNA polymerase and is known to inhibit chlamydial HSPs [33]. Other antibiotics, such as doxycycline and azithromycin, inhibit bacterial protein synthesis [34,35]. Perhaps a combined antimicrobial approach, using one antibiotic that inhibits RNA polymerase and HSPs with another that inhibits bacterial protein synthesis, could achieve successful eradication of these persistent chlamydiae leading to amelioration, or even cure, of the disease process.

Interestingly, *in vitro* data suggest that successful synergistic eradication of cells infected with persistent *Chlamydia* can be achieved with a combination of rifampin and azithromycin [36]. In this same study, neither antibiotic was efficacious when used alone. In 2004, we performed an open-label trial that suggested a 9-month course of doxycycline and rifampin was more efficacious at ameliorating the symptoms of suspected *Chlamydia*-induced ReA than doxycycline monotherapy [37]. In this trial, there was no further improvement from months 6–9 in patients taking doxycycline and rifampin. Very recently, we completed a double-blind placebo-controlled trial demonstrating that a 6-month course of the combination antibiotics (either doxycycline and rifampin, or azithromycin and rifampin) were superior to placebo at not only improving the clinical symptoms of chronic *Chlamydia*-induced ReA, but also clearing the chlamydial infection [38]. Overall, 63% of the study participants treated with combination antibiotics were responders compared with 20% of placebo-treated patients ($p = 0.01$). Further, 22% of the patients randomized to combination antibiotics went into complete remission, whereas none of the patients randomized to placebo achieved this strict end point. Although not powered to compare the two combination antibiotic regimens in a head-to-head fashion, the vast majority of participants who achieved remission were treated with azithromycin and rifampin; 33% of the subjects in this treatment group achieved remission.

Although it is too soon to determine if this combined antimicrobial therapeutic approach truly represents the pathway to a cure, these data certainly lend hope. Two studies now indicate that improvement in the clinical symptoms of *Chlamydia*-induced ReA can be achieved with

this treatment approach. One of these studies also suggests that the actual nidus of inflammation, that is, persistent chlamydiae, can be cleared with combination antibiotics and this clearance mirrors the clinical response; however, this was a secondary end point of this trial. Despite these promising results, important questions remain regarding the most efficacious combination of antibiotics as well as the proper dose and duration of this prolonged combined antimicrobial approach. Furthermore, more data regarding the clearance of these persistent chlamydiae are needed. Because the inflammation is synovial based, we need more data demonstrating definitive clearance of synovial-based chlamydiae, specifically. If synovial-based clearance is attainable, how do cytokine signatures change or how might these changes influence successful eradication? How does long-term combination antimicrobial therapy alter these cytokine profiles?

Although the above referenced trials focus specifically on *Chlamydia*-induced ReA, persistent chlamydial infections have been linked to many chronic diseases including trachoma, female infertility, coronary artery disease, asthma and certain types of cervical cancer. Although many of the links are speculative, these observations suggest a more complex role for persistent, metabolically active chlamydiae than previously thought. Combination antimicrobial therapy as a potential cure for persistent chlamydial infections would not only transform the treatment of *Chlamydia*-induced ReA, it could have important implications in many chronic diseases.

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Bibliography

1 Lee A, Fox J, Hazell S: Pathogenicity of *Helicobacter pylori*: a perspective. *Infect. Immun.* 61(5), 1601–1610 (1993).

2 Libby P, Egan D, Skarlatos S: Roles of infectious agents in atherosclerosis and restenosis. *Circulation* 96(11), 4095–4103 (1997).

3 Kol A, Bourcier T, Lichtman AH *et al.*: Chlamydial and human heat shock protein 60s activate human vascular endothelium, smooth muscle cells, and macrophages. *J. Clin. Invest.* 103(4), 571–577 (1999).

4 Li L, Messas E, Batista EL Jr *et al.*: *Porphyromonas gingivalis* infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. *Circulation* 105(7), 861–867 (2002).

5 Espinola-Klein C, Rupprecht HJ, Blankenberg S *et al.*: Impact of infectious burden on extent and long-term prognosis of atherosclerosis. *Circulation* 105(1), 15–21 (2002).

6 Whittum-Hudson JA, Gérard HC, Schumacher HR, Hudson AP: Pathogenesis of *Chlamydia*-associated arthritis. In: *Chlamydia – Pathogenesis and Treatments*. Bavoil P, Wyrick P (Eds). Blackwell Publishing Inc., Boston, MA, USA, 475–504 (2006).

7 Köhler L, Zeidler H, Hudson AP: Etiologic agents in reactive arthritis: their molecular biology and phagocyte–host interactions. *Baillière's Clin. Rheumatol.* 12, 589–609 (1998).

8 Inman RD, Whittum-Hudson JA, Schumacher HR, Hudson AP: *Chlamydia*-associated arthritis. *Curr. Opin. Rheumatol.* 12, 254–262 (2000).

9 Henry CH, Hudson AP, Gérard HC, Franco PF, Wolford LM: Identification of *Chlamydia trachomatis* in the human temperomandibular joint. *J. Oral Maxillofac. Surg.* 57(6), 683–688 (1999).

10 Cates W, Wasserheit JH: Genital chlamydial infections: epidemiology and reproductive consequences. *Am. J. Obstet. Gynecol.* 164(6 Pt 2), 1771–1781 (1991).

11 Anttila R, Saikku P, Koskela P *et al.*: Serotypes of *Chlamydia trachomatis* and risk for development of cervical squamous cell carcinoma. *J. Am. Med. Assoc.* 285(1), 47–51 (2001).

12 Hahn DL, Azenabor AA, Beatty WL, Byrne GI: *Chlamydia pneumoniae* as a respiratory pathogen. *Front Biosci.* 7, e66–e76 (2002).

13 Grayston JT: Background and current knowledge of *Chlamydia pneumoniae* and atherosclerosis. *J. Infect. Dis.* 181(Suppl. 3), S402–S410 (2000).

14 Saikku P, Leinonen M, Mattila K *et al.*: Serologic evidence of an association of a novel *Chlamydia*, TWAR, with chronic coronary heart disease and acute myocardial infarction. *Lancet* 2(8618), 983–985 (1988).

15 Belland RJ, Ouellette SP, Gieffers J, Byrne GI: *Chlamydia pneumoniae* and atherosclerosis. *Cell Microbiol.* 6(2), 117–127 (2004).

16 Sriram S, Stratton CW, Yao S *et al.*: *Chlamydia pneumoniae* infection of the central nervous system in multiple sclerosis. *Ann. Neurol.* 46(1), 6–14 (1999).

17 Gérard H, Dreses-Werringloer U, Wildt KS *et al.*: *Chlamydia (Chlamydophila) pneumoniae* in the Alzheimer's brain. *FEMS Immunol. Med. Microbiol.* 48(3), 355–366 (2006).

18 Wagner AD, Gérard HC, Fresemann T *et al.*: Detection of *C. pneumoniae* in giant cell vasculitis and correlation with the topographical arrangement of tissue-infiltrating dendritic cells. *Arthritis Rheum.* 43(7), 1543–1551 (2000).

19 Schumacher HR, Gérard HC, Arayssi TK *et al.*: *Chlamydia pneumoniae* is present in synovial tissue of arthritis patients with lower prevalence than that of *C. trachomatis*. *Arthritis Rheum.* 42(9), 1889–1893 (1999).

20 Gérard HC, Schumacher HR, El-Gabalawy H, Goldbach-Mansky R, Hudson AP: *Chlamydia pneumoniae* infecting the human synovium are viable and metabolically active. *Microb. Pathog.* 29(1), 17–24 (2000).

21 Moazed TC, Kuo CC, Grayston JT, Campbell LA: Evidence of systemic dissemination of *Chlamydia pneumoniae* via macrophages in the mouse. *J. Infect. Dis.* 177(5), 1322–1325 (1998).

22 Gérard HC, Branigan PJ, Schumacher HR, Hudson AP: Synovial *Chlamydia trachomatis* in patients with reactive arthritis/Reiter's syndrome are viable but show aberrant gene expression. *J. Rheumatol.* 25(4), 734–742 (1998).

23 Hogan, RJ Mathews SA, Mukjopadhyay S, Summersgill JT, Timms P: Chlamydial persistence: beyond the biphasic paradigm. *Infect. Immun.* 72(4), 1843–1855 (2004).

24 Gérard HC, Krauß-Opatz B, Rudy D *et al.*: Expression of *Chlamydia trachomatis* genes required for DNA synthesis and cell division in active vs persistent infection. *Mol. Microbiol.* 41(3), 731–741 (2001).

25 Belland RJ, Nelson DE, Virok D *et al.*: Transcriptome analysis of chlamydial growth during IFN-γ-mediated persistence and reactivation. *Proc. Natl Acad. Sci. USA* 100(14), 15971–15976 (2003).

26 Gerard HC, Whittum-Hudson JA, Schumacher HR, Hudson AP: Differential expression of three *Chlamydia trachomatis* hsp60-encoding genes in active vs. persistent infections. *Microb. Pathog.* 36(1), 35–39 (2004).

27 Gaston JS, Cox C, Granfors K: Clinical and experimental evidence for persistent *Yersinia* infection in reactive arthritis. *Arthritis Rheum.* 42(10), 2239–2242 (1999).

28 Clegg DO, Reda DJ, Weisman MH *et al.*: Comparison of sulfasalazine and placebo in the treatment of reactive arthritis (Reiter's syndrome). A department of veterans affairs cooperative study. *Arthritis Rheum.* 39(12), 2021–2027 (1996).

29 Flagg SD, Meador R, Hsia E, Kitumnuaypong T, Schumacher HR Jr: Decreased pain and synovial inflammation after etanercept therapy in patients with reactive and undifferentiated arthritis: an open-label trial. *Arthritis Rheum.* 53(4), 613–617 (2005).

30 Oili KS, Niinisalo H, Korpilahde T, Virolainen J: Treatment of reactive arthritis with infliximab. *Scand. J. Rheumatol.* 32(2), 122–124 (2003).

31 Haibel H, Brandt J, Rudawaleit M: Therapy of chronic enteral reactive arthritis with infliximab. *Ann. Rheum. Dis.* 62, AB0380 (2003).

32 Zugel U, Kaufmann SH: Role of heat shock proteins in protection from and pathogenesis of infectious diseases. *Clin. Microbiol. Rev.* 12(1), 19–39 (1999).

33 Engel JN, Pollack J, Perara E, Ganem D: Heat shock response of murine *Chlamydia trachomatis*. *J. Bacteriol.* 172(12), 6959–6972 (1990).

34 Amin AR, Attur MG, Thakker GD *et al.*: A novel mechanism of action of tetracyclines: effects on nitric oxide synthases. *Proc. Natl Acad. Sci. USA* 93(24), 14014–14019 (1996).

35 Retsema J, Fu W: Macrolides: structures and microbial targets. *Int. J. Antimicrob. Agents* 18(Suppl. 1), S3–S10 (2001).

36 Dreses-Werringloer U, Padubrin I, Zeidler H, Kohler L: Effects of azithromycin and rifampin on *Chlamydia trachomatis* infection *in vitro*. *Antimicrob. Agents Chemother.* 45(11), 3001–3008 (2001).

37 Carter JD, Valeriano J, Vasey FB: A prospective, randomized 9-month comparison of doxycycline vs. doxycycline and rifampin in undifferentiated spondyloarthritis – with special reference to *Chlamydia*-induced arthritis. *J. Rheumatol.* 31(10), 1973–1980 (2004).

38 Carter JD, Espinoza LR, Inman RD *et al.*: Combination antibiotics as a treatment for chronic *Chlamydia*-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial. *Arthritis Rheum.* 62(5), 1298–1307 (2010).