
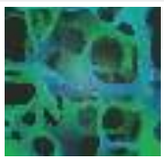


Bulletin Board

An infectious origin for rheumatic disease?

Novel research indicates that Bartonella*, the bacterial causative agent of several zoonotic diseases, may also play a role in human rheumatic disease.*

Bartonella are a genus of Gram-negative bacteria known to infect both humans and animals. Over eight species of the bacteria are known to infect humans with humans acting as both reservoir and incidental hosts. The bacteria are transmitted predominately by arthropod vectors; however, zoonotic disease can occur through direct transmission, as seen in 'cat scratch' disease.

Speaking to *Expert Review of Anti-infective Therapy*, Edward Breitschwerdt, Professor of medicine and infectious disease at North Carolina State University's College of Veterinary Medicine, CEO of Galaxy Diagnostics and co-principle investigator of the study, commented on the building scientific evidence that indicates the involvement of Bartonella in rheumatic disease, "Based upon evolving epidemiological and microbiological data, it is possible that infection with *Bartonella* species can play a role in joint pain and lameness in dogs, horses and human patients. For example, both *Bartonella henselae* and *Bartonella vinsonii* subsp. *berkhoffii* were co-isolated from joint fluid of a dog that progressed from a nonerosive to an erosive polyarthritis, indicating that direct infection of joints is possible. In addition, osteolytic lesions, at times involving bones within a joint have been reported in association with *Bartonella henselae* infection in people and *Bartonella vinsonii* subsp. *berkhoffii* infection in a cat.

Along with his fellow researchers at North Carolina State University, and in collaboration with a rheumatologist based in Maryland, Breitschwerdt's team conducted a study examining 296 immunocompetent rheumatology patients for Bartonella antibody prevalence. Patients were selected from those examined by the rheumatologist in the Maryland–Washington, DC, USA, area from August 2008 to April 2009. As *Bartonella* spp. are known to infect cells within the vascular system primarily selection was biased by patients who had evidence of small vessel disease. Also included were patients with chronic joint pain, synovial vascular inflammation or rheumatoid arthritis.

Anticoagulated blood and serum samples were collected from all patients in the study. Serum was tested for the presence of *Bartonella* antibodies through the use of a traditional immunofluorescence antibody assay utilizing various *Bartonella* spp. antigens. Molecular prevalence of Bartonella was determined using a four step enrichment blood culture PCR. All patients completed a five-page questionnaire detailing concurrent conditions, animal/arthropod exposure and further medical information.

Collated results from serology and molecular analysis demonstrated high *B. henselae*, *B. koehlerae*, and *B. vinsonii* (62%) antibody prevalences. *Bartonella* spp. bacteremia, was also high at 41%. More than half of these

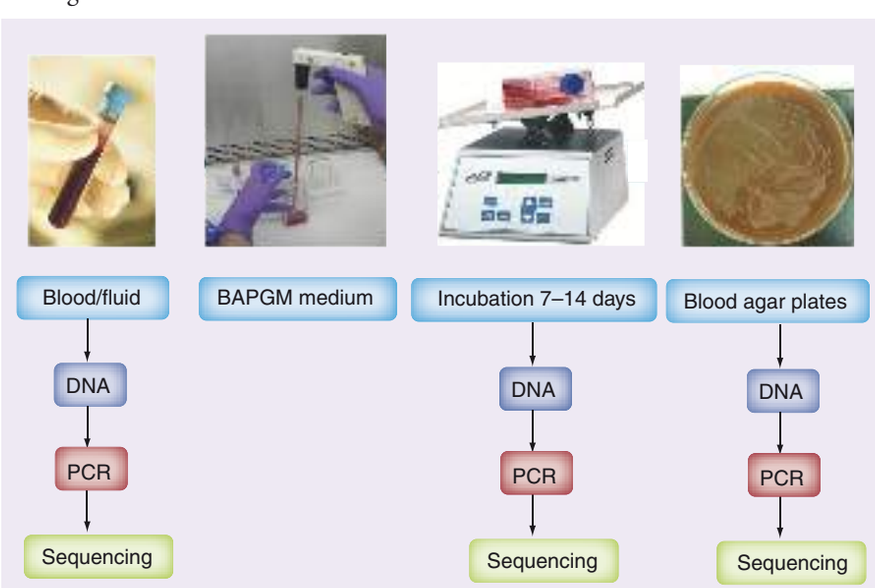

Figure 1. Description of the *Bartonella* **alpha-proteobacteria growth medium platform utilized for the detection of *Bartonella* species and other fastidious microorganisms in clinical samples**.

in the news...

patients reported a prior diagnosis of Lyme disease, bartonellosis or babesiosis although the diagnosis for many of these cases had not been previously confirmed by a medical professional.

Breitschwerdt discussed his view on the current therapeutic picture of *Bartonella* infection, "In recent years and by using a unique diagnostic platform that incorporates an optimized insect cell culture medium (Bartonella alpha Proteobacteria growth medium), our research group has published data that support the possibility of persistent intravascular infection in immunocompetent patients. Based upon sequential microbiological testing using the Bartonella alpha Proteobacteria growth medium platform, therapeutic elimination of these bacteria with antibiotics has often proven challenging. Additional studies are clearly needed to determine the frequency with which these bacteria can be found in patients with joint pain and polyarthritis and prospective studies are critically needed to determine an optimal therapeutic approach for patients with chronic *Bartonella* bacteremia."

– Written by Caroline Purslow

Source: Maggi RG, Mozayeni BR, Pultorak EL *et al.* Bartonella spp. bacteremia and rheumatic symptoms in patients from Lyme disease-endemic region. *Emerg. Infect. Dis.* 18(5), 783–791 (2012).

Study finds association between discoid lupus erythematosus and vasculitis and chronic seizures

In a report published in the May issue of *Arthritis Care & Research*, researchers found that patients with the discoid form of cutaneous lupus erythematosus typically have worse skin damage than patients with systemic lupus. In addition, the study found that these patients are also at risk for severe neurologic manifestations.

Those with the discoid form of lupus were much more likely to have extensive cutaneous scarring (OR: 14.66, 95% CI: 8.67–24.81) ad scarring alopecia (OR: 5.71, 95% CI: 3.91–8.35) according to the study investigators.

An additional unexpected finding of the study showed that discoid patients also had increased risk for development of sequelae such as chronic seizures (OR: 1.84, 95% CI: 1.08–3.13).

Discoid lupus – the most common type of cutaneous lupus – is characterized by areas of erythematosus, scaly patches and plugging of the hair follicles, usually on sun-exposed parts of the skin. It is believed that 10% of discoid lupus patients will go on to eventually develop systemic lupus.

The study was designed to examine the clinical manifestations of disease in this subset of patients. The investigators analyzed data from a longitudinal cohort of 2228 patients with SLE from multiple centers in the USA. Of the participants, a total of 43% were white, 36% were African American and smaller numbers were Hispanics fro Puerto Rico or Texas.

Those affected with discoid skin lesions were more commonly African–Americans and smokers whereas those of Texas Hispanic origin, anti-dsDNA and end-stage renal disease lowered the likelihood of discoid lupus.

"Recent data suggest that immune complexes of chromatin fragments with anti-dsDNA antibodies and their subsequent binding to the glomerular basement membrane may represent a key event in the development of nephritis," they explained.

"Our findings highlight the importance of surveillance of this population of SLE patients, particularly because of the association with serious manifestations such as vasculitis and chronic seizures," Luis M. Vilá, MD, of the University of Puerto Rico in San Juan and colleagues concluded.

Limitations of the study included a lack of consistent data on disease activity because of different measurements used in the various centers, inadequate information about the various therapies used, and unavailable data on pattern of skin involvement.

– Written by Paolo Reveglia

Source: Santiago-Casas Y, Vilá LM, McGwin Jr G *et al.* Association of discoid lupus erythematosus with clinical manifestations and damage accrual in a multiethnic lupus cohort. *Arthritis Care Res.* 64, 704–712 (2012).

Study demonstrates anti- IL-6 receptor antibody effective in slowing the progression of joint damage in rheumatoid arthritis patients

Tocilizumab, an anti-IL-6 receptor antibody, has been show to significantly slow the progression of joint damage in rheumatoid arthritis (RA) patients, even in those who continue to have active disease, a *post-hoc* analysis has revealed.

In the report published in the May issue of *Arthritis & Rheumatism*, researchers showed that after a year of treatment, patients receiving placebo plus MTX had a mean score of 21.7 on the clinical disease activity index, while those receiving TCZ plus MTX had similar mean scores of 20.2 ($p = 0.19$).

However, analysis of the data revealed a

threefold difference between the two therapies in radiographic progression – with a mean change of 1.2 points for the placebo group and only 0.4 points in the TCZ group (p = 0.0009) – on total Genant-modified sharp scores.

Previous research had demonstrated that joint damage in RA is associated with ongoing inflammation in untreated patients and even in those managed with conventional therapies. However, TNF-inhibitors have been shown to interfere with radiographic progression, even in patients who remain symptomatic or who have persistently high levels of acute phase reactants.

Josef Smolen, lead author of the study from the University of Vienna, Austria, and colleagues set out to determine whether a similar phenomenon occurs with inhibition of IL-6. In order to do so, they analyzed data from the LITHE trial, which randomized 531 patients to MTX plus either placebo or TCZ in doses of 4 or 8 mg/kg every 4 weeks for a year.

Radiographs of the hand and feet were assessed at baseline and one year. Patients randomized to receive placebo showed a significant association between progression in radiographic score and disease indices at one year (r = 0.26–0.28, p = 0.002–0.006). However, in patients receiving TCZ, x-ray progression did not correlate with any disease variable including C-reactive protein levels (r = 0.08), swollen joint counts (r = 0.007) or the simplified disease activity index (r = 0.005) with p values being nonsignificant for all comparisons according to authors.

"Taken together, these data suggested that the link between surrogate markers of disease activity and progression of joint damage could be seen in placebo-treated patients also when the [total Genant-modified Sharp score] was employed, but that [tocilizumab] treatment abrogates this association between disease activity and destruction, similar to previous reports for TNF inhibitors," they wrote.

Over the course of the study year, erosion scores changed by 0.65 points in the placebo group and 0.25 points in the tocilizumab group, while the corresponding changes in joint space narrowing were 0.53 and 0.14 points respectively.

"This finding indicates that [tocilizumab] interferes independent of disease activity with both osteoclastogenic and cartilage-degrading pathways," the researchers observed.

The authors did note, however, that the study was limited by being a *post-hoc* analysis, although the original data had been collected prospectively and by focusing on patients who completed the study.

– Written by Paolo Reveglia

Source: Smolen J, Martinez Avila JC, Aletaha D. Tocilizumab inhibits progression of joint damage in rheumatoid arthritis irrespective of its anti-inflammatory effects: disassociation of the link between inflammation and destruction. *Ann. Rheum. Dis.* 71, 687–693 (2012).

Study demonstrates positive results from Phase IIb osteoarthritis study for next generation NSAID

CrystalGenomics, Inc have achieved positive results with their candidate compound CG100649, a next generation NSAID. Both primary and secondary end points were met in the study. Over the course of 4 weeks the following properties of CG100649 were evaluated: safety, functional benefits and analgesic efficacy. CG100649 (2 or 4 mg/day) was evaluated against Celebrex® (celecoxib; 200 mg per day).

The mechanism of action of CG100649 is dual inhibition of COX-2 and carbonic anhydrase. It is a first-in-class NSAID candidate; it's interaction with the carbonic anhydrase found in red blood cells means CG100649 has a unique transport mechanism specifically to tissues that are inflamed. This localised method of delivery also means systemic exposure is kept low. As traditional NSAID and COX-2 inhibitors have safety concerns in tissue areas such as renal, cardiovascular and gastrointestinal, it is thought the dual inhibitory properties of CG100649 will possess a far superior safety profile.

The study involved patients diagnosed with osteoarthritis (OA), in a double-blind, multi-centre, randomized Phase IIb trial. All patients had a 5–14-day period where all previous medications apart from acetaminophen were washed out of the system. Subjects were asked to grade the intensity of their pain on a 0–10 numerical rating scale and those recording a moderate (4) to severe (8) recording of hip/knee OA pains were randomized into the study. Over the course of 28 days, patients received daily doses of 2 or 4 mg CG100649 or 200 mg of celecoxib.

Investigators used the standardized WOMAC OA Index and WOMAC subscales of physical function, pain and stiffness to assess anti-arthritic efficacy. The primary efficacy outcome was calculated using the WOMAC-Pain subscale to measure average change between day 28 and baseline. Secondary outcomes were measured by change in the WOMAC Pain subscale on the following days: 7, 14, 21, 35 and 42. On days 14, 28 and 42 changes in the total WOMAC OA Index were measured and changes in the WOMAC Stiffness and Physical Function were noted. On days 1, 14, 28 and 42 enrollments underwent Subject's Global Assessment and Physician's Global Assessment of OA pain.

It was reported that both CG100649 treatment groups (2 and 4 mg) showed that on all primary and secondary treatment groups; CG100649 was shown to be equivalent to celecoxib.

Neither treatment group experienced any serious adverse events. Within the short time frame CG100649 had no apparent effect on blood pressure, heart function or ECG but a long-term cardiovascular safety profile will be carried out. The doses used within this Phase IIb study also allows a dose to be selected for the Phase III trial expected to commence later in 2012.

– Written by: Priti Nagda

Source: CrystalGenomics, Inc News Room: www.cgxinc.com.

Depression & anxiety common in arthritis sufferers

Arthritis is a condition that has unfortunate and disabling consequences. It is not uncommon for sufferers to experience depression, anxiety or both. According to Louise B Murphy from the Centers for Disease Control and Prevention, every one in three arthritis sufferer also encounters depression and anxiety. Out of the two, anxiety appears to be more prevalent; as seen in the study 'Anxiety is more common than depression among US adults with arthritis' authored by Murphy *et al.* Their study comprised of 1793 adults over the age of 45 years who had been doctor-diagnosed with arthritis or another type of rheumatic condition such as osteoarthritis. The sample was lifted from the Arthritis Conditions and Health Effects Survey (a random digit dialed telephone interview survey).

Study author Murphy, stated: "What we ultimately took away is that we've usually thought of arthritis as a condition that can have such profound disabling consequences. But what came out here is how profound the emotional consequences are. This is a call to action." The study has been published in Arthritis Care and Research.

The method of obtaining information from the study participants was via a questionnaire from which the answers were used to determine their mental state of health. The results were surprising to researchers undertaking the study. From the data collated it appeared that approximately one third of the 1793 adults revealed they suffered from either depression or anxiety.

Although researchers had expected to see depression was being suffered it was the fact that the other mental health condition, anxiety, was nearly twice as high as depression. The surprise came to the researchers as amongst arthritis researchers there is more emphasis and attention towards depression.

This made sense to Dr Eric Gall, director of the Arthritis Center at the University of Arizona, who explained; 'These people have chronic pain, and that breeds depression. They're frightened about the disease; they're frightened about being crippled and not being able to do things. They have problems with their marriages and jobs and so forth.'

From the findings of the study carried out Murphy and colleagues it is recommended that arthritis patients be screened for mental health conditions, such as depression and anxiety. This is because although these conditions are occurring in high prevalence, there are effective therapeutic options available to help those patients. As arthritis patients either do not seek the treatment for their mental health or their conditions are not detected by healthcare providers currently the opportunity to improve the quality of these patients' lives is being missed.

– Written by Priti Nagda

Source: Murphy LB, Sacks JJ, Brady TJ, Hootman JM, Chapman DP. Anxiety is more common than depression among US adults with arthritis. *Arthritis Care Res. (Hoboken)* doi: 10.1002/acr.21685 (Epub ahead of print).

Study results shows potential for ankylosing spondylitis treatment

Results from a proof-of-concept study have demonstrated that secukinumab, an IL-17 pathway targeting, fully human monoclonal antibody, has potential in the treatment of moderate-to-severe ankylosing spondylitis. This study abstract was presented at the British Society of Rheumatology with Paul Emery (Academic Unit of Musculoskeletal Medicine, University of Leeds, UK) as first author.

Ankylosing spondylitis is one of the three most common forms of inflammatory arthritis, along with rheumatoid arthritis and psoriatic arthritis. According to the National Ankylosing Spondylitis Society, typical symptoms of the condition include, "slow or gradual onset of back pain and stiffness over weeks or months, rather than hours or days," "early-morning stiffness and pain, wearing off or reducing during the day with exercise" and "weight loss, especially in the early stages." Arthritis Research UK states that, "Ankylosing spondylitis affects 2–3-times as many men as women and it's most likely to start in your 20s and 30s."

Scientists thought that a therapeutic avenue could possibly be discovered by disturbing the IL-17 pathway. This speculation was due to the fact that previous research highlighted a specific genetic association (HLA-B27) seen in most ankylosing spondylitis patients results in an increase in the production of IL-23, and IL-23 then mediates the IL-17 pathway through T-cells.

In this 28-week, double-blind, placebo-controlled study, patients were administered two 10 mg/kg intravenous (i.v.) does of the antibody (does given 3 weeks apart). Patients taking part in the study may have previously received up to three disease-modifying antirheumatic drugs, and furthermore, 50% of the participants had received treatment with a TNF inhibitor. Trial participants were permitted to continue on stable does of methotrexate, prednisone, and other such medications.

Investigators found that by week 6, 14 out of the 23 patients receiving two does of secukinumab had shown a 20% improvement. This is in comparison to one out of six patients receiving placebo demonstrating the same level of improvement. It was noted that 92% of patients that received the antibody remained in the study to its completion and 35% of patients demonstrated a 40% improvement in accordance with the Assessment of SpondyloArthritis International Society

(ASAS) response criteria. A total of 35% of patients received a response in five out of six core ASAS criteria and according to Emery, "The responses were really quite striking in some cases."

The average decrease in the ankylosing spondylitis disease activity index was 1.8 and in *post-hoc* analysis of subgroups investigators found "superior response rates with TNFi naive patients (11 out of 13; 85%) compared with TNFi pre-exposed patients (3 out of 10; 30%)." No deaths were reported in the study and authors write that the incidence of adverse events were similar to those observed in previous secukinumab studies.

Study investigators used a Bayesian method in order to analyze the primary end point and included data from other patients treated with placebo from eight previously conducted studies with ankylosing spondylitis patients. This meant that a reduced number of placebo participants were required in the present study. Emery explains, "This is a major advance in clinical trial design, because it minimizes patient exposure to drugs that may not work. A number of cancer drugs are being developed using Bayesian statistical methods."

Authors of the study conclude, "Data presented here suggest that secukinumab may be useful for the treatment of active ankylosing spondylitis and thereby warrant larger long-term studies on safety and efficacy."

– Written by xxx

Sources: Emery P, Baeten D, Sieper J et al. Evaluation of efficacy and safety of secukinumab in the treatment of patients with moderate-to-severe ankylosing spondylitis Rheumatology 51(Suppl. 3), iii19–iii26; Medpage Today: www.medpagetoday.com/Rheumatology/BSR/32449; National Ankylosing Spondylitis Society: www.nass.co.uk/about-as/; Arthritis Research UK: www.arthritisresearchuk.org/arthritis-information/conditions/ankylosing-spondylitis.aspx

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact:

Paolo Reveglia, Commissioning Editor, *International Journal of Clinical Rheumatology*, Future Medicine Ltd,
Unitec House, 2 Albert Place, London N3 1QB, UK
Tel.: +44 (0)20 8371 6090;
p.reveglia@futuremedicine.com