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Antibacterial Therapy Induces Remission in Sarcoidosis

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ABSTRACT

At least five studies have identified a special kind of antibiotic-resistant bacteria in the biopsy specimens from sarcoid patients, yet, until recently, an effective therapy has remained elusive. The nature of the infestation is atypical, with electron-microscopy showing polymorphic bacteria actually living within the phagocytic cells of the immune system itself. When the bacteria are killed, their endotoxin is therefore released directly

into the infected phagocytes. The resulting Jarisch-Herxheimer Shock is debilitating, and, for some patients, life-threatening. It persists as long as the parasites are being killed, often for a year or more. Two hormones mediate the body's endotoxin-induced Th1 immune response - Angiotensin II and 1,25-dihydroxyvitamin-D. Blockade of type AT1 Angiotensin receptors can rapidly relieve the patients' symptomatic suffering and minimize the risk of life-threatening cardiac events, especially bradycardia. Combinations of the bacteriostatic antibiotics Azithromycin, Minocycline and Sulfamethoxazole/Trimethoprim have been particularly effective at killing these cell-dwelling bacteria. It is critical that the dose of antibiotic is kept to a minimum, so that the amount of endotoxin release does not overwhelm the ability of the patient to tolerate the resulting Jarisch-Herxheimer Shock.

Introduction

Cantwell [1] recently reviewed 3 decades of studies which reported the isolation of pleomorphic, acid-fast, Cell Wall Deficient (CWD) bacteria in the biopsy specimens from sarcoidosis patients. Moscovic first identified these pleomorphic bacteria in sarcoid tissue in 1978 [2,3] followed by Cantwell [4,5,6], Mattman [7] and Nilsson, et al, [8].

Wirostko, et al, [9] used a transmission electron microscope to produce stunning photographs of CWD coccoid bacterial forms in the immune cells from the vitreous of the eyes of 4 sarcoidosis patients with chronic uveitis. Their photographs documented parasitized monocytes, lymphocytes, and polymorphonuclear leucocytes.

Parasitized monocytes and polymorphonuclear leucocytes

The dimer protein NuclearFactor-kappaB (NF-kB) is at the heart of the Th1 immune response of Sarcoidosis. Normally NF-kB is stabilized in the cytoplasm of the monocytes, macrophages, dendritic cells, and polymorphonuclear leucocytes which form the central region of a sarcoid granuloma. When NF-kB is activated to move to the nucleus of these cells, a messenger RNA is released which initiates the cytokine cascade, including release of the cytokine 'TNF-alpha'. Glucocorticoids (such as prednisone) exert their immunomodulatory effect by blocking this activation of NF-kappaB [10].

NF-kB is normally activated to move to the nucleus in response to a variety of receptors located on the cell periphery. In a healthy individual the NF-kB activation is typically triggered by activated Lymphocytes. However, if there are bacteria living within the cytoplasm of the cell, then these bacteria can render the lymphocytes redundant, and trigger the NF-kB to initiate a cytokine release based solely upon proteins released by the bacteria itself [11,12].

Once there are bacteria living within the cells of the immune system, then one is not dealing with an immune system which is subject to the same mechanisms of pathogen identification and reaction which occur in a healthy individual. One is dealing with a run-

away immune reaction totally dominated by the parasitic bacteria. The consequent run-away inflammation forms the granuloma of sarcoidosis.

What Species of Bacteria are Involved?

There are many (>60) species of bacteria which have been isolated in a CWD or mycoplasmal form. Species already identified in sarcoidosis patients include Borrelia [13], Mycobacterium [14], Rickettsia [8] and Propionibacterium [15].

We believe that no one lymphopenic pathogen is solely responsible for sarcoid inflammation, but that a variety of species are typically present in any given patient. We note that our antibacterial therapy usually progresses in steps. As the antimicrobial cocktails and concentrations are varied throughout a therapy, patients experience pain due to JHS in different organs, in different regions of the body. It is rare for the same antibiotic combination to be effective both against inflammation in the eyes, for example, and inflammation in the lungs [16].

The CWD bacteria are present in the bloodstream of both healthy individuals and sarcoidosis patients [18,19]. It is clear that genetic predisposition causes some folks to become sick with the autoimmune disorders [17], while the majority of the population remains healthy [20,21].

Where do these CWD bacteria come from?

The initial pathway for infection with these bacteria is most probably from mother to child. McPherson Brown noted their presence in the birth canal [20], and Sanchez confirmed a high rate of mother-to-child infection with at least one species of mycoplasma [21].

These bacteria can survive the temperatures used in commercial pasteurization of milk [22]. So it is clear that they can pass through the food chain. They have been shown only partly susceptible to the typical sterilization processes used in the commercial water supply [23].

Many of the CWD coccoid forms are so small that they pass through the 0.2 micron filters typically used in pharmaceutical production. It can be expected that CWD contaminants are present in pharmaceuticals, especially in biologic preparations and vaccines.

CWD coccoid bacteria are ubiquitously formed by bacterial organisms as a protective response to antibiotics whose mode of action is to attack the bacterial cell wall.

For example, the antibiotic Rifampin is used to combat Tuberculosis. Although it is well known that mycobacteria quickly develop resistance to Rifampin (this is the reason it is almost always combined with Isoniazid), it is not so well known that at least one mechanism for resistance to Rifampin is for the mycobacteria to morph into these tiny

CWD L-forms. There is no longer any cell wall for the Rifampin to attack. This adaptation has been confirmed in-vitro [24].

The ubiquitous use of Penicillins also creates these antibiotic-resistant CWD bacteria. Penicillins attack bacterial cell walls, and these CWD pleomorphs have been observed forming in-vitro, under the action of Penicillins [25].

Finally, the immune system itself creates some of these resistant bacteria whenever it fights active infections. Borrelia burgdorferi have been observed morphing to these tiny cystic forms in spinal fluid, and then changing back to active spirochetes in less hostile environments [26].

Bacterial antibodies and cultures

The characteristic of sarcoid granuloma is that they are non-caseating, non-necrotic. A granuloma is a healthy collection of living cells. There is little apoptosis, and thus little necrosis. The lifetime of infected macrophages is in excess of 40 days, and turnover is low. Consequently very few bacteria die and enter the bloodstream. That low concentration is detectable with PCR technology [14], but PCR requires specific primers for each species to be detected. The wide variety of species makes it very difficult to perform a definite diagnosis using PCR alone.

Cantwell and Mattman successfully cultured the CWD species they isolated from their patients [27,7]. Cantwell has privately communicated the difficulties he experienced while culturing these CWD bacteria. He reported that they are very slow-growing. The typical minimum time to culture was 3 months, with 6-9 months not unusual [27]. There was always the risk of contamination, especially when incubating for such lengthy periods. Based on his observations, we do not expect that cultures will become useful diagnostic tools when dealing with CWD bacteria.

Jarisch-Herxheimer Shock

Antibacterial therapies aimed at killing these intra-cellular microbes have to contend with Jarisch-Herxheimer Shock (JHS) [28,29], "Jarisch-Herxheimer-Lukashevich syndrome" [30]. Mangin writes "patients are reporting periodic aggravation of their symptoms as an apparent direct response to the antibiotics .. these patients say that their treatment makes them feel much worse before they experience symptom-relief" [31].

Thus, JHS is at once a bad thing, because it exacerbates the suffering of the patient, and also a good thing, because it indicates that the bacteria are being effectively killed. In fact, it is our observation that those patients who do not experience significant JHS are not killing the bacteria at a rate fast enough to induce remission of their sarcoid inflammation. Out of our current subject cohort (n>100) only 5 patients have had significant difficulty finding an effective antibiotic regimen, and all have eventually been 'privileged' to suffer the effects of JHS.

Indeed, the greatest danger is that too powerful an antibiotic regimen will be put in place too soon, precipitating life-threatening JHS. Even while exercising great care, we have had two patients with life-threatening bradycardia and several with (temporary) debilitating pulmonary insufficiency. The two bradycardia events each lasted about two months and disappeared as the JHS subsided. In both cases the bradycardia was controlled with high doses of the Angiotensin Receptor Blocker, Olmesartan Medoxomil (Benicar/Olmetec).

A number of cases of skin rash have developed in subjects upon commencing the antibiotic therapy. For example, one subject reported that a skin rash was exacerbated when commencing the initial (minocycline) phase of the therapy. It cleared after 4 months but returned again (in a milder presentation) when Azithromycin was added. It disappeared again after another 3 months, and has not subsequently returned.

The hormones Angiotensin II and 1,25-dihydroxyvitamin-D

We have previously proposed "the Angiotensin Hypothesis", describing the endocrine biochemistry of the Th1 immune reaction as being dependent upon the hormone Angiotensin II and the secosteroid hormone 1,25-dihydroxyvitamin-D (1,25-D) [32,33]

Nearly all (>80%) of our sarcoidosis cohort initially exhibited a 1,25-D level in excess of the Merck Maximum of (45 pg/ml) [34]. Their levels were also higher than the plus-two-sigma point of the distribution derived from the Danish population study [35]. 1,25-D has proven by far the best indicator of systemic sarcoid inflammation, and the best indication of the degree of JHS that a patient can exhibit when starting antibiotic therapy. Anecdotally, we take values of 1,25-D over 60 pg/ml to indicate that extra caution will be necessary, and values over 80 pg/ml warn of likely cardiac involvement.

A low value of 1,25-D indicates an invalid assay result (most frequently because the serum was not frozen before being sent to the lab) or the presence of a comorbid condition that shifts the body's Th1 response towards a Th2 immune condition. Typical diseases which significantly lower the 1,25-D value include fungal infections and cancers, especially Breast Cancer[36] and Malignant Melanoma [37], as well as viral diseases such as Hepatitis-C and AIDS [38].

Blockade of Type AT1 Angiotensin Receptors has been critical in reducing the additional inflammation and potential fibrosis caused by the endotoxin release [33]. Surprisingly, there is a large difference in efficacy between the available Angiotensin Receptor Antagonists. We have found only Olmesartan Medoxomil (Benicar/Olmetec) to be totally effective, while Valsartan and Irbesartan are much less effective. Commencing Olmesartan at the therapeutic minimum of 40mg every 8 hours significantly reduces the value of serum 1,25-D, in some cases halving the value within 14 days. The ARB also seems to make the bacteria more susceptible to the antibiotics.

As we hypothesized in an earlier paper [17] we believe that the inability of sarcoidosis patients to properly control surges in their paracrine 1,25-D production is one of the

predisposing factors which allows the bacteria to initially parasitize the phagocytes.

Antibiotic and Dosing Guidelines

It is clear that the bacteria causing sarcoid inflammation do not succumb to the antibiotics that are in common usage. If this were the case, then the bacterial pathogenesis of sarcoidosis would have become obvious long ago, based on unexpected 'spontaneous remission' concurrent with antibiotic therapies for other conditions.

Partly this is because many of the species do not succumb to any one antibiotic (they are 'antibiotic-resistant') and partly it is because the dosing regimes in common usage do not work well when treating the bacteria populating the immune system of sarcoid patients.

Minocycline is the only antibiotic monotherapy that can usually be relied upon to start reducing a sarcoid patient's bacterial load. But Minocycline's action against the intra-cellular bacteria is not achieved with normal dosing regimens. As noted by Brown [20], Minocycline is most effective when its concentration in the bloodstream is allowed to decay between successive doses. With a pharmacokinetic half-life around 17 hours, the dosing schedule proposed by Brown (of Monday, Wednesday and Friday) meets that criteria. We have also used a 48 hour interval in our own dosing guidelines, depending on the preferences of the individual patient. The starting dose of Minocycline should be no greater than 25mg every 48 hours. Even this low dosage has caused significant breathing difficulties for some of the most severely ill patients. We suggest increasing the dose based on the patient's ability to tolerate the JHS, and we try to maintain the patients on Minocycline (alone) for the first three months of therapy. It is important to note that Doxycycline is not effective on as wide a spectrum of bacteria as Minocycline. In particular, Doxycycline seems ineffective against the aerobic bacteria that populate the lungs. It is our opinion that Doxycycline should not be used in any therapy for Sarcoidosis.

When the patient can tolerate the JHS resulting from 100mg of Minocycline every 48 hours, we add one quarter of a 250mg Azithromycin tablet (=62mg), once a week. We find it generally takes several months before the average patient is able to gradually increase the Azithromycin dosage to a full 250mg weekly, while maintaining 100mg of minocycline every 48 hours. At this point a little Sulfamethoxazole/Trimethoprim can be added to the 48 hour Minocycline to potentiate activity against additional resistant species [39].

Typical Timelines

Based on our observation of the progress of our initial cohort [16], at about 3 months into therapy, most subjects have achieved sufficient symptomatic relief to guarantee their compliance with the remainder of the antibiotic regimens. At about 6 months, most subjects report relief from fatigue, somnolence and insomnia, and report that their memory is returning. Useful bloodwork markers are 1,25-D, Alkaline Phosphatase, Triglycerides, and C-Reactive Protein. All should have started to improve by month 6. By

the end of the first year, Imaging should show reduced adenopathy, and most bloodwork will have returned to within normal range. Even though most subjects have achieved 'remission' at around 18 months, we currently anticipate that antibiotic therapy will need to be continued well beyond that, until all species have succumbed to the antimicrobials. Peripheral neuropathy seems to have the slowest resolution, with little progress within the first 6 months.

Summary

Bachelez, et al, [40] were the first to show that Tetracyclines were capable of inducing remission in sarcoidosis. When we discussed the Bachelez study with Alan Cantwell [1] he contributed valuable insights into the bacteria he had seen under his microscope. Barbara Wirostko [9] suggested trying Azithromycin. We added our Angiotensin Hypothesis, along with a heterogeneous group of 50 sarcoidosis patients (presenting pulmonary, neurological and cutaneous involvement) and put together the study [16,17] that formed the basis for the observations in this paper.

The subjects in our cohort variously reported regaining cognitive focus, stamina, and stable gait, and resolving chronic pain, paresthesias and visual disturbances. Some were able to discard wheelchairs, braces and supplementary oxygen.

There still is so much to learn about the idiopathic inflammatory diseases, but at last we are making progress...

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