Cimetidine as a novel adjunctive treatment for early stage Lyme disease

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Abstract

Lyme disease, caused by the spirochete Borrelia burgdorferi (Bb), is the most common vector-borne illness in the United States. It is a complex disease which may affect the skin, joints, heart, eyes, and central nervous system. Prompt diagnosis and treatment is curative in most instances. However, a significant percentage of patients experience ongoing symptoms after treatment. Currently, there is much controversy regarding the diagnosis, pathophysiology, and treatment of Lyme disease. Pathogen persistence despite treatment lies at the heart of this debate.

Many believe that the ongoing symptoms are due to factors such as autoimmunity or permanent damage that is incurred during the active infection. However, there is an emerging school of thought that states that ongoing symptoms are due to a persistent infection that is able to survive both the immune response and antibiotic therapy. Numerous studies have shown that Bb can indeed persist within the host despite treatment and several mechanisms have been proposed to explain Bb’s persistence capabilities. These include: polymorphism, antigenic variance, biofilm formation, persister cells, and immunomodulation.

There is evidence that Bb is able to alter cytokine profiles within the host which may allow the organism to survive the immune response. This immunomodulation follows a pattern of T-helper 1 (TH1) suppression in favor of T-helper 2 (TH2) processes. In contrast, it has been shown that the optimal immune response to Bb infection involves an early, robust TH1 response and a later conversion to TH2 dominance once the infection is controlled or cleared. It has been proposed that a reconstitution of proper immune-competency in the infected host may improve clinical outcomes in Lyme disease.

Cimetidine (CIM) is an over-the-counter histamine-2 (H2) antagonist that is primarily used to lower acid secretions in the stomach. T-regulatory (Treg) cells also possess the H2 receptor, which has spurred interest in CIM as a potential immunomodulator. CIM therapy has been shown to increase levels of the TH1 associated cytokines IL-12, TNF-α, and IFN-γ while decreasing levels of the TH2 associated cytokine IL-10. The author proposes a novel theory that CIM therapy during early Bb infection may promote a more appropriate immune response and increase the utility of antibiotic therapy during early stage Lyme disease, thus improving clinical outcomes of the disease.

Introduction

The spirochete Borrelia burgdorferi (Bb) is the causative agent of Lyme disease, which is the most common vector-borne illness in the United States [1]. It was once believed to be primarily a musculoskeletal disease, although it is now known that multisystemic manifestations are common. Symptoms often reflect involvement of the skin, joints, heart, and nervous system [2]. Patients may also complain of constitutional symptoms such as fatigue, pain, paresthesias, anxiety, depression, malaise, trouble concentrating, and cognitive difficulties [3]. Prompt identification and treatment of Lyme disease typically results in cessation of symptoms in the patient. However, standard treatment failures do occur [4] and it is estimated that ten to twenty percent of patients continue to have persistent symptoms despite antibiotic therapy [5]. In addition, patients may not be aware of a tick bite or may not develop the tell-tale bulls-eye rash, which can delay a proper diagnosis and possibly lead to a persistent infection that becomes difficult to treat using standard practices.

The exact mechanism of how the microbe is able to persist in an immunocompetent host isn’t fully understood. However, a number of theories have been presented and are backed by intriguing evidence. These include biofilm production [6], persister cell formation [7] sequestration in immune-privileged sites [8], alteration of surface proteins [9], inactivation of complement system...
regulatory proteins [10], and immunomodulation [11]. Bb has also been shown to take on different pleomorphic states such as L-forms and cyst-forms when presented with an unfavorable environment [12,13]. There exists the possibility that the microbe uses a combination of the above tactics to evade host immune responses and persist within the host.

It has been well documented that both ticks and Bb are able to modulate the host’s immune response in such a way that favors dissemination and persistence of the microbe [14,15]. As such, restoration of a more effective immune response is an attractive strategy for preventing microbe persistence and chronic disease. In this current conceptual paper, the author attempts to lay out the case that cimetidine (CIM), an over-the-counter histamine-2 (H2) receptor antagonist sold under the trade name Tagamet®, may be able to counteract the immune-modulating effects of both Bb and lookeed ticks. In addition to its marketed biological effects, CIM has been studied for its various effects on immune function. It is theorized here that CIM therapy, in conjunction with antibiotic therapy, may lead to more favorable outcomes in patients diagnosed with early stage (less than 3 months post tick bite) Lyme disease.

The need for a new approach

There is no doubt that Lyme disease has a large impact on society. In fact, the Centers for Disease Control (CDC) released estimates in 2013 stating that the number of annual cases in the U.S. is approximately 300,000 [16]. This is roughly a ten-fold increase compared to previous estimates [17] and clearly shows that Lyme disease is a larger problem than previously thought. Due to the often non-specific clinical presentation of the disease, proper diagnosis can be challenging. Individuals who are not properly treated early in the course of infection may go on to develop chronic symptoms, which can have a profoundly negative impact on quality of life. For example, a study on the quality of life status of chronic Lyme disease patients revealed functional deficits that are comparable to those of congestive heart failure patients [18].

There is much debate regarding whether ongoing symptoms following standard treatment are due to persistent infection or some form of immunopathology. Lyme-induced autoimmunity cannot be ruled out; however, a number of scientific studies have shown that Bb can indeed persist within a host despite antibiotic therapy [19]. Given the possibility that a subset of Lyme disease patients will go on to develop chronic disease due to persistent infection, there exists a need for a treatment that can work synergistically with antibiotic agents to aid in the elimination of the infection.

CIM has been shown to augment certain functions that reflect activity of the cellular arm of the immune system [20]. Conversely, both lookeed tick saliva and Bb infection have been shown to inhibit cellular immunity [14]. This allows the microbe to disseminate, take up residence, and persist in host tissues if the infection is not treated promptly. Using an ex vivo model, Diterich et al. found that white blood cells exposed to Bb displayed an attenuated release capacity of pro-inflammatory cytokines, thus weakening the cellular immune response. The authors concluded that “reconstitution of the immunocompetence of the patients represents an attractive target for supportive treatment to antibiosis in chronic Lyme disease” [21]. If CIM’s effects were able to counteract the immunomodulation induced by lookeed tick saliva and/or Bb exposure, it may provide a safe, low cost addition to standard antibiotic therapy in the early stages of the disease.

Bb persistence

Embers et al. characterized the proposed mechanisms of Bb persistence within the immunocompetent human host into two categories: active immune suppression and immune evasion [11]. Table 1 further describes this anergy.

In addition to the above mechanisms, it was recently found that Bb is able to form persister cells that are highly tolerant to antibiotics [22]. After screening an FDA approved drug library, it was found that only a three drug combination consisting of daptomycin, cefoperazone, and doxycycline was able to eradicate these Bb persisters in vitro [22].

In a 2011 editorial paper, Stricker and Johnson [13] identified twenty-six studies cited in a comprehensive review of the Infectious Disease Society of America’s (IDSA) treatment guidelines [23], which found that Bb is able to persist within a human host despite treatment. Table 2 lists these studies along with their characteristics.

These studies give credence to the possibility of persistent infection despite antibiotic therapy. More recent studies by Embers et al. [50] and Hodzick et al. [51] have also shown Bb’s persistence capabilities despite treatment in macaques and mice respectively.

Table 1

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<th>Proposed mechanisms of Bb persistence.</th>
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<td><strong>Immune suppression</strong></td>
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<td>Innate</td>
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<td>Complement inhibition</td>
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<td>Induction of anti-inflammatory Cytokines</td>
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<td>Toleration of monocytes</td>
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Table 2

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<th>Research displaying Bb persistence in humans despite antibiotic therapy.</th>
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<td><strong>Author</strong></td>
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<td>Weber et al. [24]</td>
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<td>Schmidli et al. [25]</td>
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<td>Battafarano et al. [42]</td>
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<td>Bayer et al. [48]</td>
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Key: PCR = polymerase chain reaction, CSF = cerebrospinal fluid.
T-cells drive the immune response

T-cell functions are a crucial aspect in the host's immune response to infection. There are also a target for immunomodulation by the Bb organism \([11]\). T-cells can generally be divided into three categories: T-helper cells, cytotoxic T-cells, and T-regulatory cells \((Treg\text{ cells})\) \([52]\). In addition, T-helper cells can be further divided into T-helper1 cells \((TH1\text{ cells})\) and T-helper2 cells \((TH2\text{ cells})\) \([52]\). TH1 cells activate the cytotoxic T-cells, neutrophils, and macrophages that are involved in cell-mediated immunity and potentiate tissue inflammation \([53]\). TH2 cells activate B-cells, which produce the antibodies that are involved in the humoral immune response and provide long term immunologic protection \([53]\). Treg cells help regulate the TH1/TH2 balance through the secretion of cytokine chemical messengers \([53]\).

The cytokines IL-12 and IFN-\(\gamma\) promote TH1 cell formation, while IL-4 and IL-10 promote TH2 cell formation \([54–57]\). When an antigen is presented to a naïve T-helper cell, the cell differentiates down a particular pathway depending on which cytokines are present. The resulting mature T-helper cells then go on to produce their respective effector cytokines. If IL-12 and IFN-\(\gamma\) are in high concentrations, the cell will become a TH1 cell \([54,55]\). Conversely, if IL-4 and IL-10 are present in high concentrations, the cell will become a TH2 cell \([56,57]\). In addition to promoting TH2 cell development, TH2 associated cytokines also inhibit TH1 cell development \([58]\). For example, IL-10 is a potent inhibitor of TH1 cell differentiation and has been shown to inhibit secretion of the TH1 associated cytokines IL-2 and IFN-\(\gamma\) \([59]\).

Tick-host interactions

Bb is transmitted when an infected host attaches to and feeds on a host. Transmission requires a complex interaction between the pathogen, vector, and host. Tick saliva contains a wide array of enzymes that are able to modulate the host's immune response \([15]\). In order to successfully feed for prolonged periods without harm, ticks have developed the ability to down-regulate the host's innate immune response \([15]\). Consequently, this allows for safe passage of the Bb pathogen into the host \([60]\) and conversely, prevention of this immunomodulation could prevent Bb transmission and its subsequent proliferation.

In 1996, Zeidner et al. found that treating mice with the TH1 associated cytokine TNF-\(\alpha\) during tick feeding provided a 95% protection rate against transmission \([61]\). The study also showed that IFN-\(\gamma\) administration offered a 55% protection rate. A year later, the researchers showed that both tick saliva and Bb infection down-regulate the TH1 associated cytokines IL-2 and IFN-\(\gamma\), while up-regulating the TH2 associated cytokine IL-4 in disease-susceptible C3H mice \([62]\). In contrast, disease-resistant BALB/c mice resisted this immunomodulatory mechanism. The authors concluded that control of this TH2 deviation could play a role in preventing Bb transmission in a murine model. Zeidner and colleagues further confirmed this model in 2008 when they showed that reconstituting a TH1 bias by neutralizing IL-4 prior to tick feeding prevented Bb transmission to mice \([63]\). Another study found that prostaglandin E2, a constituent of Ixodes ticks saliva, inhibits the production of the TH1 associated cytokines IL-12 and TNF-\(\alpha\) by dendritic cells \([64]\). The culmination of this information suggests that tick saliva inhibits the host's TH1 response in favor of a TH2 deviated response and these actions promote the transmission of Bb from vector to host.

Immunomodulation by the Lyme disease pathogen

In order to persist within any host, a microbe inevitably has to evade the host’s immune system. Immunomodulation is one such strategy that Bb uses to evade the immune response. It has been proposed that the optimal host mechanism for infection clearance in early Lyme disease is a strong TH1 response \([65–67]\). To counteract this, Bb uses a number of strategies. One of these strategies is the induction of cytokine imbalances that promote immune dysregulation. These imbalances follow a pattern of TH1 suppression in favor of TH2 activity. For instance, acute Bb infection produces a strong up-regulation of the TH2 associated cytokine IL-10 \([68,69]\), which down-regulates TH1 responses \([59,70]\) and has also been shown to induce immune tolerance to the Bb organism \([71]\). In a murine model, researchers also found that anti IL-10 therapy produced decreased spirochete counts in biopsied tissues \([72]\).

Other cytokine shifts have also been found in studies that investigated the organism's effects on the functions of various leukocytes. Diterich et al. studied the cytokine secretion profiles of leukocytes after exposure to Bb in vitro \([21]\). They found that leukocytes from chronic Lyme disease patients produced lower levels of the TH1 associated cytokines TNF-\(\alpha\) and IFN-\(\gamma\) compared to leukocytes from healthy controls. In another study, patients who had recovered from Lyme disease were also found to have increased numbers of TNF-\(\alpha\) secreting dendritic cells and higher levels of IL-12 in whole blood when compared to patients that developed chronic symptoms \([66]\). Similar results were found by Wildhe et al. when they examined the cerebrospinal fluid (CSF) cytokine profiles of infected patients \([73]\). They found that patients who developed chronic neuroborreliosis (neurologic Lyme disease) displayed lower CSF levels of TNF-\(\alpha\) early in the disease course compared to patients who went on to recover.

Yrjänäinen et al. showed that TNF-\(\alpha\) may play a particularly important role in controlling early stage Bb infection \([74]\). One third of mice that were treated with ceftriaxone and anti-TNF-\(\alpha\) were found to harbor viable spirochetes at fourteen weeks post-infection. In contrast, no viable spirochetes could be detected in mice that received only ceftriaxone. Additional evidence of the importance of a strong TH1 response in pathogen clearance was displayed in a model that induced a TH2 deviation. This was accomplished by exposing mice to inorganic mercury, a potent driver of TH2 dominance. The mercury-exposed mice showed a decrease in arthritis severity, but also a decrease in the ability to clear the infection \([75]\). The authors concluded that a strong TH1 response is required for optimal elimination of the Bb pathogen.

Some researchers have postulated that while an initial TH1 response is important for the control of Bb infection, prolonged TH1 associated inflammation may be responsible for the persistent symptoms experienced by chronic Lyme disease patients \([76–78]\). For example, an initial increase in the TH1 associated cytokine IFN-\(\gamma\) followed by up-regulation of the TH2 associated cytokine IL-4 was found to be associated with disease clearance. In contrast, prolonged IFN-\(\gamma\) secretion was associated with chronic disease \([67]\). These findings seem to indicate that an overly robust TH1 immune response may be responsible for the development of chronic Lyme disease. However, in a later study, Wildhe et al. states that a strong, early TH1 response may be required for the system to switch to a TH2 response later on \([79]\). In other words, a sufficient TH1 development and therefore an increase in FOXP3 mRNA indicates an increased TH2 activity \([81]\). This finding suggests that chronic
Cimetidine: a new weapon in the fight?

CIM is an H2 receptor antagonist with the primary marketed physiological effect of reducing acid secretion in the stomach. The Food and Drug Administration (FDA) approved the drug for use in duodenal ulcer disease, Zollinger-Ellison syndrome, and other gastrointestinal (GI) hyper-secretory conditions. CIM has a large amount of research supporting its pharmacological properties and safety profile and was at one time the top selling drug in the world. Due to its immunomodulatory properties, a number of off label uses have been proposed for the drug over the years. These include the treatment of certain cancers, herpes zoster and dermatological conditions such as common warts, genital warts, urticaria, and mastocytosis. It has also been studied as a potential adjuvant in vaccines.

The discovery that Treg cells possess the H2 receptor prompted various investigations into CIM’s effect on immune function. Blockage of the Treg H2 receptor suppresses this T-cell’s functional capabilities and has been shown to up-regulate TH1 associated immune parameters and enhance cellular immunity. This occurs because histamine, through its action on Treg cells, suppresses TH1 cell differentiation and augments TH2 cell differentiation. Therefore, blocking the Treg H2 receptor pushes undifferentiated T-helper cells down the TH1 pathway and thus works to enhance cellular immunity. CIM’s action on Treg cells has been shown to alter cytokine profiles in vivo. In an open label study of CIM’s effectiveness in the treatment of recalcitrant warts, examination of biopsies revealed increased levels of IL-2 and IFN-γ at lesion sites. In 2008, Wang et al. studied the use of CIM as an adjuvant in hepatitis B vaccines. Using a murine model, the authors found that the vaccines containing CIM significantly increased IL-12 and IFN-γ levels while decreasing IL-10 levels. A similar study showed that CIM-containing hepatitis B vaccines augmented cell-mediated immune responses. IL-12 and TNF-α levels were found to be elevated and IL-10 levels were shown to be decreased compared to controls.

CIM spurred interest as an anti-cancer drug after a 1988 study by Burtin et al. showed that the drug improved survival times six fold in gastric cancer patients. A review on this subject in 1999 found that the benefits of CIM regarding gastric cancer outcomes were due in part to its inhibitory effects on Treg cell activity and subsequent stimulation of cell-mediated immunity. Another review in 2011 found that CIM’s anti-cancer actions were due to tumor cell adhesion interference, angiogenesis disruption, and immune modulation. With regard to its immunologic properties, CIM was shown to increase the levels of a number of cytokines including IFN-γ and TNF-α. It was also shown to increase natural killer cell activity and the antigen presenting capabilities of dendritic cells.

Much of the research done on CIM’s effect on the immune system was conducted on patients who were hospitalized. This model is of interest because hospitalized patients may be immune-compromised due to injury, illness, or surgery and are at risk for nosocomial infections. Adams et al. showed that CIM therapy was able to preserve cell-mediated immune function after colon resection surgery. In a study of intensive care unit patients, administration of intravenous CIM significantly increased the level of the TH1 associated cytokine IL-12. Another study examined CIM’s effects on the cellular immune system following cardiopulmonary bypass surgery. The authors concluded that the drug was able to counteract the depressive effects of surgery on cellular immunity and may prevent post-operative infections.

The preceding data suggests that CIM is able to effectively and reliably reverse immunosuppression of cell-mediated immunity through increases in TH-1 associated cytokine levels brought on by its antagonistic action on the Treg cell H2 receptor.

Immunomodulatory properties of CIM

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Discussion

Despite conventional treatment methods, the Lyme disease pathogen may be able to persist within the host and go on to cause chronic disease. The clinical outcome of Lyme disease appears to be influenced by the type of immune response mounted during the early stages of disease, as suggested by various human and animal models. This is evidenced by a 2014 study by Soloski et al. that identified two distinct subpopulations among acute Lyme disease patients with regard to immunological responses. The two groups, termed “mediator-high” and “mediator-low,” differed in levels of serum inflammatory mediators (T-cell chemokines and acute phase proteins) as well as lymphocyte status, seroconversion status, liver enzyme status, and total number of symptoms. The “mediator-low” group appears to represent a proportion of patients who are immunologically hyporesponsive to acute Bb infection. This important finding falls in line with Bb’s known immunomodulatory properties and may help explain why some patients go on to develop chronic disease.

A pharmacological “nudging” of the system toward a more appropriate immune response may be what is required to prevent Bb’s evasion of the immune system and subsequent persistence. One of the mechanisms that Bb uses to evade the host’s immune response is the modulation of certain parameters of the immune system. This includes suppression of TH1 activity, especially early on in the disease. Chronic Lyme disease patients have displayed decreased secretion capabilities of IL-12, TNF-α, and IFN-γ, all of which are required for TH1 processes. Bb has also been shown to be a strong inducer of IL-10, which inhibits TH1 activity and may contribute to immune tolerance of the Bb organism.

Research suggests that a strong TH1 response early on in the infection is important for the control and clearance of the pathogen. If this early TH1 response is insufficient to control the infection, chronic disease may result despite treatment. This could be due to ongoing antigenic stimulation, which prolongs TH1 associated inflammation and prevents a conversion to TH2 activity. As described previously, the conversion to a cytokine profile that indicates TH2 dominance is positively associated with recovery from the disease. There exists the possibility that once dissemination occurs, the body cannot be completely cleared of the microbe using standard practices. In this scenario, TH2 conversion, with its resultant protective antibody production, may be required to keep this low-level infection at bay while tamping down the tissue-damaging inflammation that can be brought on by chronic TH1 stimulation.

CIM has shown the ability to increase levels of the TH1 associated cytokines IL-12, TNF-α, and IFN-γ while decreasing the TH2 associated cytokine IL-10. These actions lie in direct opposition to the immunomodulatory effects of both Bb and Bb infection. Furthermore, CIM has been shown to increase CD57 natural killer cell counts, which may be negatively impacted by Bb infection. This information leads to a proposed mechanism in
which high dose (800–1600 mg per day) CIM therapy may be able to counteract the immunomodulatory effects of *Bb* tick saliva and prevent the transmission and dissemination of *Bb*. As previously stated, administration of TNF-α and IFN-γ during tick feeding provided a 95% and 55% protection rate respectively against *Bb* transmission in mice. If CIM were to be taken prophylactically after recognition of a tick bite, it may be able to ramp up production of TNF-α and IFN-γ (as well as other TH1 associated cytokines) and prevent or limit the transmission of bacteria from vector to host.

It is also proposed here that high dose CIM therapy, in conjunction with antibiotic therapy, may be able to help control *Bb* infection in its early stages by neutralizing *Bb* induced immune dysregulation and enhancing the body's cell-mediated immune response. These actions could possibly prevent the spirochetes from gaining access to deeper tissues and employing further mechanisms that promote persistence and chronic disease (i.e. biofilms, persister cell formation, intracellular localization). CIM therapy may have the capability to boost TH1 activity in the crucial early stages of disease, which could aid in the control of the infection and set the stage for a TH2 conversion later on. This conversion could then place the system in the optimal state for providing long term, antibody-mediated protection from a resurgence of infection and clinical relapse while also attenuating the chronic inflammation that may be induced by a prolonged TH1 immune response to a small number of relatively benign surviving microbes.

A method of preventing chronic Lyme disease would have a profound impact on society given the scope of this illness (300,000 annual cases of infection) and the disability that may result (functional deficits comparable to congestive heart failure). If ten to twenty percent of infected patients develop persistent symptoms, as is estimated, this would potentially equal 30,000–60,000 cases of chronic Lyme disease per year. If even a percentage of these cases could be prevented by taking a safe, low cost, over-the-counter medication, it could save millions of dollars in healthcare costs and lost productivity as well as prevent untold suffering.

Initial proof-of-concept research should involve in vivo murine studies on the effectiveness of CIM to prevent *Bb* transmission following tick attachment as well as CIM’s ability to augment clearance of the microbe at various stages of infection (i.e. pre and post dissemination).

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