Cimetidine as a novel adjunctive treatment for early stage Lyme disease

Justin Shemenski *

D'Youville College, 320 Porter ave, Buffalo, NY 14201, United States

ARTICLE INFO

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.

© 2016 Elsevier Ltd. All rights reserved.

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 multi-systemic 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

* Address: 257 Glenview Dr, New Kensington, PA 15068, United States
E-mail address: Shemej25@dyc.edu

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 *Ixodes* 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 *Ixodes* 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 *Ixodes* 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
Proposed mechanisms of *Bb* persistence.

Immune suppression		Immune evasion	
Innate	Adaptive	Antigenic variation	Physical seclusion
Complement inhibition	Tolerization of lymphocytes	Gene conversion	Intracellular invasion
Induction of anti-inflammatory Cytokines	Induction of anti-inflammatory Cytokines	Mutation and recombination	Cyst forms
		Variable expression of antigens	Immuno-privileged sites
Tolerization of monocytes	Sequestration of antibodies in immune complexes		

Table 2
Research displaying *Bb* persistence in humans despite antibiotic therapy.

Author	Year	Origin	Method	Sample
Weber et al. [24]	1988	Europe	Histology	Brain, liver
Schmidli et al. [25]	1988	Europe	Culture	Synovial fluid
Cimmino et al. [26]	1989	Europe	Histology	Spleen
Preac-Mursic et al. [27]	1989	Europe	Culture	Skin, CSF
Pfister et al. [28]	1991	Europe	Culture	CSF
Strle et al. [29]	1993	Europe	Culture	Skin
Preac-Mursic et al. [30]	1993	Europe	Culture	Iris
Haupl et al. [31]	1993	Europe	Culture	Ligament
Strle et al. [32]	1996	Europe	Culture	Skin
Preac-Mursic et al. [33]	1996	Europe	Culture	Skin, CSF
Oksi et al. [34]	1996	Europe	Culture	CSF
			PCR	Brain
Priem et al. [35]	1998	Europe	PCR	Synovial fluid
Breier et al. [36]	2001	Europe	Culture	Skin
Hunfeld et al. [37]	2005	Europe	Culture	Skin
Hudson et al. [38]	1998	Australia	Culture, PCR	Skin
Steere et al. [39]	1988	USA	Histology	Synovial fluid
Kirsch et al. [40]	1988	USA	Histology	Lung
Liegner et al. [41]	1993	USA	Histology	Skin
			PCR	Blood
Battafarano et al. [42]	1993	USA	Histology, PCR	Synovial fluid
Chancellor et al. [43]	1993	USA	Histology	Bladder
Nocton et al. [44]	1994	USA	PCR	Synovial fluid
Shadick et al. [45]	1994	USA	Histology	Brain
Masters et al. [46]	1994	USA	Culture	Blood
Lawrence et al. [47]	1995	USA	PCR	CSF
Bayer et al. [48]	1996	USA	PCR	Urine
Nocton et al. [49]	1996	USA	PCR	CSF

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. They 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 cells) [52]. In addition, T-helper cells can be further divided into T-helper1 cells (TH1) and T-helper2 cells (TH2) [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-γ 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-γ 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-γ [59].

Tick-host interactions

Bb is transmitted when an infected *Ixodes* tick 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-α during tick feeding provided a 95% protection rate against transmission [61]. The study also showed that IFN-γ 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-γ, 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* tick saliva, inhibits the production of the TH1 associated cytokines IL-12 and TNF-α 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-α and IFN-γ 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-α 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-α early in the disease course compared to patients who went on to recover.

Yrjänäinen et al. showed that TNF-α 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-α 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-γ followed by up-regulation of the TH2 associated cytokine IL-4 was found to be associated with disease clearance. In contrast, prolonged IFN-γ 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, Widhe 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 response is needed to clear *Bb* from the system (or at least control it). This allows for an up-regulation of TH2 activity, which then suppresses TH1 processes along with the TH1 associated inflammation and leads to a resolution of symptoms.

Other immune markers have also been shown to be affected by *Bb* infection. Jerefors et al. found a decrease in the number of *Bb*-specific IFN-γ and IL-12 secreting cells along with an increase in *Bb*-specific cells expressing forkhead boxP3 (FOXP3) mRNA in patients with chronic Lyme disease compared to asymptomatic *Bb* exposed individuals [80]. FOXP3 is required for Treg cell development and therefore an increase in FOXP3 mRNA indicates an increase in Treg cell activity [81]. This finding suggests that chronic

Lyme disease patients have an increase in Treg cell activity, which may promote *Bb* tolerance by inhibiting the TH1 response.

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 (i.e. acid reflux disease) in 1977 [82]. 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 [82]. 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 [83], herpes zoster [84,85] and dermatological conditions such as common warts, genital warts, urticaria, and mastocytosis [86]. It has also been studied as a potential adjuvant in vaccines [87,88]. The off label usage of CIM typically involves higher dosages than what is used for GI conditions. The majority of investigational studies utilized dosages of between 800 mg/d and 1600 mg/d for human subjects, while the typical dosage for GI symptoms is between 400 mg/d and 800 mg/d.

Immunomodulatory properties of CIM

The discovery that Treg cells possess the H2 receptor [89] prompted various investigations into CIM's effect on immune function [90]. 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 [91,92]. This occurs because histamine, through its action on Treg cells, suppresses TH1 cell differentiation and augments TH2 cell differentiation [93,94]. Therefore, blocking the Treg cell 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 [95]. In 2008, Wang et al. studied the use of CIM as an adjuvant in hepatitis B vaccines [96]. 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 [87]. 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. that showed that the drug improved survival times sixfold in gastric cancer patients [97]. 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 [98]. Another review in 2011 found that CIM's anti-cancer actions were due to tumor cell adhesion interference, angiogenesis disruption, and immune modulation [83]. 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 [83].

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 [99]. Adams et al. showed that CIM therapy was able to preserve cell-mediated immune function after colon resection surgery [100]. In a study of intensive care unit patients, administration of intravenous CIM significantly increased the level of the TH1 associated cytokine IL-12 [101]. Another study examined CIM's effects on the cellular immune system following cardiopulmonary bypass surgery [102]. 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.

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 [103]. 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 *Ixodes* ticks and *Bb* infection. Furthermore, CIM has been shown to increase CD57 natural killer cell counts, which may be negatively impacted by Bb infection [104]. 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 *Ixodes* 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).

References

[1] Bacon RM, Kugeler KJ, Mead PS. Surveillance for Lyme disease–United States, 1992–2006. MMWR Surveillance Summaries 2008;57(10):1–9.

[2] Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43(9):1089–134.

[3] Cameron D, Gaito A, Harris N, et al. Evidence-based guidelines for the management of Lyme disease. Expert Rev Anti Infect Ther 2004;2(1 Suppl):S1–13.

[4] Oksi J, Marjamäki M, Nikoskelainen J, Viljanen MK. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med 1999;31(3):225–32.

[5] Marques A. Chronic Lyme disease: a review. Infect Dis Clin North Am 2008;22:341–60.

[6] Sapi E, Bastian SL, Mpoy CM, et al. Characterization of biofilm formation by Borrelia burgdorferi in vitro. PLoS ONE 2012;7(10):e48277.

[7] Sharma B, Brown A, Lewis, K. Persister formation in Borrelia burgdorferi. In: Paper presented at: 114th General Meeting of the American Society of for Microbiology; May 17–20, 2014. Boston, MA, USA.

[8] Klempner MS, Noring R, Rogers RA. Invasion of human skin fibroblasts by the Lyme disease spirochete, Borrelia burgdorferi. J Infect Dis 1993;167(5):1074–81.

[9] Zhang JR, Hardham JM, Barbour AG, Norris SJ. Antigenic variation in Lyme disease Borreliae by promiscuous recombination of VMP-like sequence cassettes. Cell 1997;89(2):275–85.

[10] Hellwage J, Meri T, Heikkilä T, et al. The complement regulator factor H binds to the surface protein OspE of Borrelia burgdorferi. J Biol Chem 2001;276(11):8427–35.

[11] Embers ME, Ramamoorthy R, Philipp MT. Survival strategies of Borrelia burgdorferi, the etiologic agent of Lyme disease. Microbes Infect 2004;6(3):312–8.

[12] Preac Mursic V, Wanner G, Reinhardt S, Busch U, Marget W. Formation and cultivation of Borrelia burgdorferi spheroplast-L-form variants. Infection 1996;24(3):218–26.

[13] Alban PS, Johnson PW, Nelson DR. Serum-starvation-induced changes in protein synthesis and morphology of Borrelia burgdorferi. Microbiol (Reading, Engl) 2000;146:119–27 (Pt 1).

[14] Zeidner N, Mbow ML, Dolan M, Massung R, Baca E, Piesman J. Effects of Ixodes scapularis and Borrelia burgdorferi on modulation of the host immune response: induction of a TH2 cytokine response in Lyme disease-susceptible (C3H/HeJ) mice but not in disease-resistant (BALB/c) mice. Infect Immun 1997;65(8):3100–6.

[15] Hovius JW. Spitting image: tick saliva assists the causative agent of Lyme disease in evading host skin's innate immune response. J Invest Dermatol 2009;129(10):2337–9.

[16] Kuehn BM. CDC estimates 300,000 US cases of Lyme disease annually. JAMA 2013;310(11):1110.

[17] Reported cases of Lyme disease by year, United States, 2002–2011. Centers for Disease Control and Prevention Website. <http://www.cdc.gov/lyme/stats/charttables/reportedcases_statelocality.html>. Updated Sept 12, 2012. Accessed Aug 19, 2012.

[18] Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 2001;345(2):85–92.

[19] Stricker RB, Johnson L. Lyme disease: the next decade. Infect Drug Resistance 2011;4:1–9.

[20] Gifford RR, Voss BV, Schmidtke JR, Ferguson RM. Histamine type-2 receptor antagonist immune modulation. I. Increased cell-mediated cytotoxicity in normal and in down-regulated systems. Surgery 1988;103(2):184–92.

[21] Diterich I, Härter L, Hassler D, Wendel A, Hartung T. Modulation of cytokine release in ex vivo-stimulated blood from borreliosis patients. Infect Immun 2001;69(2):687–94.

[22] Sharma B, Brown AV, Matluck NE, Hu LT, Lewis K. Borrelia burgdorferi, the causative agent of Lyme disease, forms drug-tolerant persister cells. Antimicrob Agents Chemother 2015;59(8):4616–24.

[23] Lantos PM, Charini WA, Medoff G, et al. Final report of the Lyme disease review panel of the Infectious Diseases Society of America. Clin Infect Dis 2010;51(1):1–5.

[24] Weber K, Bratzke HJ, Neubert U, Wilske B, Duray PH. Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatr Infect Dis J 1988;7(4):286–9.

[25] Schmidli J, Hunziker T, Moesli P, Schaad UB. Cultivation of Borrelia burgdorferi from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. J Infect Dis 1988;158(4):905–6.

[26] Cimmino MA, Azzolini A, Tobia F, Pesce CM. Spirochetes in the spleen of a patient with chronic Lyme disease. Am J Clin Pathol 1989;91(1):95–7.

[27] Preac-Mursic V, Weber K, Pfister HW, et al. Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection 1989;17(6):355–9.

[28] Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KMJ. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. Infect Dis 1991;163(2):311–8.

[29] Strle F, Preac-Mursic V, Cimperman J, Ruzic E, Maraspin V, Jereb M. Azithromycin versus doxycycline for treatment of erythema migrans: clinical and microbiological findings. Infection 1993;21(2):83–8.

[30] Preac-Mursic V, Pfister HW, Spiegel H, et al. First isolation of Borrelia burgdorferi from an iris biopsy. J Clin Neuroophthalmol 1993;13(3):155–61.

[31] Haupl T, Hahn G, Rittig M, et al. Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum 1993;36(11):1621–6.

[32] Strle F, Maraspin V, Lotric-Furlan S, Ruziç-Sabljiç E, Cimperman J. Azithromycin and doxycycline for treatment of Borrelia culture-positive erythema migrans. Infection 1996;24(1):64–8.

[33] Preac-Mursic V, Marget W, Busch U, Pleterski Rigler D, Hagl S. Kill kinetics of Borrelia burgdorferi and bacterial findings in relation to the treatment of Lyme borreliosis. Infection 1996;24(1):9–16.

[34] Oksi J, Kalimo H, Marttila RJ, et al. Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature. Brain 1996;119(6):2143–54.

[35] Priem S, Burmester GR, Kamradt T, Wolbart K, Rittig MG, Krause A. Detection of Borrelia burgdorferi by polymerase chain reaction in synovial membrane, but not in synovial fluid from patients with persisting Lyme arthritis after antibiotic therapy. Ann Rheum Dis 1998;57(2):118–21.

[36] Breier F, Khanakah G, Stanek G, et al. Isolation and polymerase chain reaction typing of Borrelia afzelii from a skin lesion in a seronegative patient with generalized ulcerating bullous lichen sclerosus et atrophicus. Br J Dermatol 2001;144(2):387–92.

[37] Hunfeld KP, Ruzic-Sabljic E, Norris DE, Kraiczy P, Strle F. In vitro susceptibility testing of Borrelia burgdorferi sensu lato isolates cultured from patients with erythema migrans before and after antimicrobial chemotherapy. Antimicrob Agents Chemother 2005;49(4):1294–301.

[38] Hudson BJ, Stewart M, Lennox VA, et al. Culture-positive Lyme borreliosis. Med J Aust 1998;168(10):500–2.

[39] Steere AC, Duray PH, Butcher EC. Spirochetal antigens and lymphoid cell surface markers in Lyme synovitis. Comparison with rheumatoid synovium and tonsillar lymphoid tissue. Arthritis Rheum 1988;31(4):487–95.

[40] Kirsch M, Ruben FL, Steere AC, Duray PH, Norden CW, Winkelstein A. Fatal adult respiratory distress syndrome in a patient with Lyme disease. JAMA 1988;259(18):2737–9.

[41] Liegner KB, Shapiro JR, Ramsay D, Halperin AJ, Hogrefe W, Kong L. Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting Borrelia burgdorferi infection. J Am Acad Dermatol 1993;28(2 pt 2):312–4.

[42] Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. Chronic septic arthritis caused by Borrelia burgdorferi. Clin Orthopaedics 1993;297:238–41.

[43] Chancellor MB, McGinnis DE, Shenot PJ, Kiilholma P, Hirsch IH. Urinary dysfunction in Lyme disease. J Urol 1993;149(1):26–30.

[44] Nocton JJ, Dressler F, Rutledge BJ, Rys PN, Persing DH, Steere AC. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis. N Engl J Med 1994;330(4):229–34.

[45] Shadick NA, Phillips CB, Logigian EL, et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Internal Med 1994;121(8):560–7.

[46] Masters E. Spirochetemia after continuous high-dose oral amoxicillin therapy. Infect Dis Clin Practice 1994;3:207–8.

[47] Lawrence C, Lipton RB, Lowy FD, Coyle PK. Seronegative chronic relapsing neuroborreliosis. Eur Neurol 1995;35(2):113–7.

[48] Bayer ME, Zhang L, Bayer MH. Borrelia burgdorferi DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. Infection 1996;24(5):347–53.

[49] Nocton JJ, Bloom BJ, Rutledge BJ. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in cerebrospinal fluid in Lyme neuroborreliosis. J Infect Dis 1996;174(3):623–7.

[50] Embers ME, Barthold SW, Borda JT, et al. Persistence of Borrelia burgdorferi in Rhesus macaques following antibiotic treatment of disseminated infection. PLoS ONE 2012;7(1):e29914.

[51] Hodzic E, Feng S, Holden K, Freet KJ, Barthold SW. Persistence of Borrelia burgdorferi following antibiotic treatment in mice. Antimicrob Agents Chemother 2008;52(5):1728–36.

[52] Nester EW, Anderson DG, Roberts CE, Nester MT. Microbiology: a human perspective. 5th ed. Boston, MA: McGraw-Hill; 2007.

[53] Parham P. The immune system. 3rd ed. New York, NY: Garland Science, Taylor & Francis Group; 2009.

[54] Schmitt N, Ueno H. Regulation of human helper T cell subset differentiation by cytokines. Curr Opin Immunol 2015;34:130–6.

[55] Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen specific adaptive immunity. Annu Rev Immunol 1995;13:251–76.

[56] Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations. Annu Rev Immunol 2010;28:445–89.

[57] Liu L, Rich BE, Inobe J, Chen W, Weiner HL. Induction of Th2 cell differentiation in the primary immune response: dendritic cells isolated from adherent cell culture treated with IL-10 prime naive CD4+ T cells to secrete IL-4. Int Immunol 1998;10(8):1017–26.

[58] Skapenko A, Niedobitek GU, Kalden JR, Lipsky PE, Schulze-koops H. Generation and regulation of human Th1-biased immune responses in vivo: a critical role for IL-4 and IL-10. J Immunol 2004;172(10):6427–34.

[59] Fiorentino DF, Zlotnik A, Vieira P, et al. IL-10 acts on the antigen-presenting cell to inhibit cytokine production by TH1 cells. J Immunol 1991;146 (10):3444–51.

[60] Wikel SK. Tick modulation of host immunity: an important factor in pathogen transmission. Int J Parasitol 1999;29(6):851–9.

[61] Zeidner N, Dreitz M, Belasco D, Fish D. Suppression of acute Ixodes scapularis-induced Borrelia burgdorferi infection using tumor necrosis factor-alpha, interleukin-2, and interferon-gamma. J Infect Dis 1996;173(1):187–95.

[62] Zeidner NS, Schneider BS, Rutherford JS, Dolan MC. Suppression of TH2 cytokines reduces tick-transmitted Borrelia burgdorferi load in mice. J Parasitol 2008;94(3):767–9.

[63] Sá-nunes A, Bafica A, Lucas DA, et al. Prostaglandin E2 is a major inhibitor of dendritic cell maturation and function in Ixodes scapularis saliva. J Immunol 2007;179(3):1497–505.

[64] Sjöwall J, Fryland L, Nordberg M, et al. Decreased TH1-type inflammatory cytokine expression in the skin is associated with persisting symptoms after treatment of erythema migrans. PLoS ONE 2011;6(3):e18220.

[65] Sjöwall J, Carlsson A, Vaarala O, et al. Innate immune responses in Lyme borreliosis: enhanced tumour necrosis factor-alpha and interleukin-12 in asymptomatic individuals in response to live spirochetes. Clin Exp Immunol 2005;141(1):89–98.

[66] Widhe M, Jarefors S, Ekerfelt C, et al. Borrelia-specific interferon-gamma and interleukin-4 secretion in cerebrospinal fluid and blood during Lyme borreliosis in humans: association with clinical outcome. J Infect Dis 2004;189(10):1881–91.

[67] Nardelli DT, Callister SM, Schell RF. Lyme arthritis: current concepts and a change in paradigm. Clin Vaccine Immunol 2008;15(1):21–34.

[68] Giambartolomei GH, Dennis VA, Philipp MT. Borrelia burgdorferi stimulates the production of interleukin-10 in peripheral blood mononuclear cells from uninfected humans and rhesus monkeys. Infect Immun 1998;66(6):2691–7.

[69] Yin Z, Braun J, Neure L, et al. T cell cytokine pattern in the joints of patients with Lyme arthritis and its regulation by cytokines and anticytokines. Arthritis Rheum 1997;40(1):69–79.

[70] Diterich I, Rauter C, Kirschning CJ, Hartung T. Borrelia burgdorferi- induced tolerance as a model of persistence via immunosuppression. Infect Immun 2003;71(7):3979–87.

[71] Brown JP, Zachary JF, Teuscher C, Weis JJ, Wooten RM. Dual role of interleukin-10 in murine Lyme disease: regulation of arthritis severity and host defense. Infect Immun 1999;67(10):5142–50.

[72] Widhe M, Grusell M, Ekerfelt C, Vrethem M, Forsberg P, Ernerudh J. Cytokines in Lyme borreliosis: lack of early tumor necrosis factor-alpha and transforming growth factor-beta-1 responses are associated with chronic neuroborreliosis. Immunology 2002;107(1):46–55.

[73] Yrjänäinen H, Hytönen J, Song XY, Oksi J, Hartiala K, Viljanen MK. Anti-tumor necrosis factor-alpha treatment activates Borrelia burgdorferi spirochetes 4 weeks after ceftriaxone treatment in C3H/He mice. J Infect Dis 2007;195 (10):1489–96.

[74] Ekerfelt C, Andersson M, Olausson A, Bergström S, Hultman P. Mercury exposure as a model for deviation of cytokine responses in experimental Lyme arthritis: HgCl2 treatment decreases T helper cell type 1-like responses and arthritis severity but delays eradication of Borrelia burgdorferi in C3H/HeN mice. Clin Exp Immunol 2007;150(1):189–97.

[75] Mckisic MD, Redmond WL, Barthold SW. Cutting edge: T cell-mediated pathology in murine Lyme borreliosis. J Immunol 2000;164(12):6096–9.

[76] Keane-myers A, Nickell SP. T cell subset-dependent modulation of immunity to Borrelia burgdorferi in mice. J Immunol 1995;154(4):1770–6.

[77] Gross DM, Steere AC, Huber BT. T helper 1 response is dominant and localized to the synovial fluid in patients with Lyme arthritis. J Immunol 1998;160 (2):1022–8.

[78] Widhe M, Skogman BH, Jarefors S, et al. Up-regulation of Borrelia-specific IL-4- and IFN-y-secreting cells in cerebrospinal fluid from children with Lyme neuroborreliosis. Int Immunol 2005;17(10):1283–91.

[79] Jarefors S, Janefjord CK, Forsberg P, Jenmalm MC, Ekerfelt C. Decreased up regulation of the interleukin-12 R beta @-chain and interferon gamma secretion and increased number of forkhead box P3- expressing cells in patients with history of chronic Lyme borreliosis compared to asymptomatic Borrelia exposed individuals. Clin Exp Immunol 2007;147(1):18–27.

[80] Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science 2003;299(5609):1057–61.

[81] Freston JW, Cimetidine I. Developments, pharmacology, and efficacy. Ann Int Med 1982;97(4):573–80.

[82] Kubecova M, Kolostova K, Pinterova D, Kacprzak G, Bobek V. Cimetidine: an anticancer drug? Eur J Pharm Sci 2011;42(5):439–44.

[83] Miller A, Harel D, Laor A, Lahat N. Cimetidine as an immunomodulator in the treatment of herpes zoster. J Neuroimmunol 1989;22(1):69–76.

[84] Bense L, Marcusson JA, Ramsten T. Effect of cimetidine on herpes zoster infection. Drug Intell Clin Pharm 1987;21(10):803–5.

[85] Scheinfeld N. Cimetidine: a review of the recent developments and reports in cutaneous medicine. Dermatol Online J 2003;9(2):4.

[86] Zhang W, Wang J, Su B, et al. Cimetidine augments TH1/TH2 dual polarized immune responses to recombinant HBV antigens. Vaccine 2011;29(29–30):4862–8.

[87] Li MJ, Lei JH, Wang T, et al. Cimetidine enhances the protective effect of GST DNA vaccine against Schistosoma japonicum. Exp Parasitol 2011;128 (4):427–32.

[88] Melmon KL, Bourne HR, Weinstein J, Sela M. Receptors for histamine can be detected on the surface of selected leukocytes. Science 1972;177 (4050):707–9.

[89] Mavligit GM. Immunologic effects of cimetidine: Potential uses. Pharmacotherapy 1987;7(6):120S–4S.

[90] Kumar A. Cimetidine: an immunomodulator. DICP 1990;24(3):289–95.

[91] Sahasrabudhe DM, Mccune CS, O'donnell RW, Henshaw EC. Inhibition of suppressor T lymphocytes (Ts) by cimetidine. J Immunol 1987;138 (9):2760–3.

[92] Packard KA, Khan MM. Effects of histamine on TH1/TH2 cytokine balance. Int Immunopharmacol 2003;3(7):909–20.

[93] Elenkov IJ, Webster E, Papanicolaou DA, Fleisher TA, Chrousos GP, Wilder RL. Histamine potently suppresses human IL-12 and stimulates IL-10 production via H2 receptors. J Immunol 1998;161(5):2586–93.

[94] Mitsuishi T, Iida K, Kawana S. Cimetidine treatment for viral warts enhances IL-2 and IFN-gamma expression but not IL-18 expression in lesional skin. Eur J Dermatol 2003;13(5):445–8.

[95] Wang J, Su B, Ding Z, Du X, Wang B. Cimetidine enhances immune response of HBV DNA vaccination via impairment of the regulatory function of regulatory T cells. Biochem Biophys Res Commun 2008;372(3):491–6.

[96] Burtin C, Noirot C, Scheinmann P, Galoppin L, Domagoj S, Bernard P. Clinical improvement in advanced cancer disease after treatment combining histamine and H2 histaminics (ranitidine or cimetidine). Eur J Cancer Clin Oncol 1988;24(2):161–7.

[97] Siegers CP, Andresen S, Keogh JP. Does cimetidine improve prospects for cancer patients? A reappraisal of the evidence to date. Digestion 1999;60 (5):415–21.

[98] Salo M. Effects of anaesthesia and surgery on the immune response. Acta Anaesthesiol Scand 1992;36(3):201–20.

[99] Adams WJ, Morris DL, Ross WB, Lubowski DZ, King DW, Peters L. Cimetidine preserves non-specific immune function after colonic resection for cancer. Aust NZ J Surg 1994;64(12):847–52.

[100] Ishikura H, Fukui H, Takeyama N, Tanaka T. Cimetidine activates interleukin-12, which enhances cellular immunity. Blood 1999;93(5):1782–3.

[101] Katoh J, Tsuchiya K, Osawa H, et al. Cimetidine reduces impairment of cellular immunity after cardiac operations with cardiopulmonary bypass. J Thorac Cardiovasc Surg 1998;116(2):312–8.

[102] Soloski MJ, Crowder LA, Lahey LJ, Wagner CA, Robinson WH, Aucott JN. Serum inflammatory mediators as markers of human Lyme disease activity. PLoS ONE 2014;9(4):e93243.

[103] Stricker R, Winger E. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. Immunol Lett 2001;76(1):43–8.