

Listeria Infection during Biologic Therapy: An Update

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Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: November 8, 2016

Revised: December 8, 2016

Accepted: December 12, 2016

Published online: February 21, 2017

ABSTRACT

The therapeutic use of biological agents such as anti tumor necrosis factor-alpha drugs carries on an increased risk of reactivation of bacterial infections. Among these, listeriosis is a particularly dreadful infection in that may be associated with septic complications such as meningitis and encephalitis and a relatively high mortality rate.

This article will discuss listeria infections in patients treated with biological agents.

Key words: Anti-TNF alfa agents; Biological therapy; Inflammatory bowel disorders; Listeriosis; Sepsis

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Casella G, Antonelli E, Villanacci V, Bachetti F, Torti G, Dore MP, Bassotti G. Listeria Infection during Biologic Therapy: An Update. *Journal of Gastroenterology and Hepatology Research* 2017; 6(1): 2261-2264 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1921>

INTRODUCTION

The therapy with anti tumor necrosis factor (TNF)-alpha agents such as infliximab, adalimumab, golimumab, etanercept is to date an established approach for several rheumatologic and gastrointestinal diseases; however, such therapy is associated to an increased risk of reactivating granulomatous diseases and other intracellular bacterial infections where the host defenses are macrophage dependent^[1]. Thus, Listeriosis may develop more frequently in patients receiving anti TNF-alpha therapies^[1].

MICROBIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS

Listeria monocytogenes is a gram positive, anaerobic, short rod-like bacterium with a median incubation period of 35 days (range 1 to 91 days). The contact with this bacterium happens through ingestion of foods such as soft or unpasteurized cheese, unwashed vegetables, and uncooked meat^[2]. Also water tanks contaminated by swallows may be a source of infection^[3] and we must always consider the failure of basic sanitation measures in Industry, particularly the special condition of food served in hospitals where a strict control is needed in food preparation to avoid the bacterium's transmission to vulnerable individuals^[3]. Listeriosis is considered a relatively rare infection in adults^[4], and it is regarded as an opportunistic infection affecting principally subjects with malignancy and/or on immunosuppressive therapy^[4], as well as pregnant women,

newborns and elderly subjects^[4]. A human disease caused by *Listeria monocytogenes* was described for the first time in 1929 by Nyfeldt^[5]; however, the mechanisms of *Listeria* infection have not been clearly elucidated yet^[1]. TNF-alpha has an important role as a defense against intracellular organism such as *Listeria*, by increasing the number of macrophages and the amount of nitric oxide in the involved area, both of paramount importance for microbial killing^[6]. The immunity to *Listeria* is mediated through T-cell lymphokine activation of macrophages; the latter are responsible for and determinant to clear *Listeria* from the blood^[7]. Soulat *et al*^[8] reported that the host DEAD-box RNA helicase DDX3X may be considered a “key component” involved in the transcriptional induction of a type 1 IFN response to Listeriosis infection. Soulat *et al*^[8] reported the mice deficient for DDX3X show a complex immune imbalance with increased predisposition to Listeriosis infection for a reduced production of cytokines and INF-gamma and impaired maturation of lymphoid lineage determining a reduction in Natural Killer (NK) cell population^[8].

The therapeutical use of anti TNF-alpha agents impairs the effect of endogenous TNF-alpha and it may promote the development of Listeriosis^[9], since *Listeria monocytogenes* DNA has been found in the intestine of inflammatory bowel disease (IBD) patients and in control subjects^[10]. Thus, mucosal damage in IBD patients with intestinal presence of *Listeria* may represent a predisposing condition to develop systemic Listeriosis during anti-TNF therapy, due to bacterial invasion from the gut to the bloodstream^[10], since it has been suggested that the intestine may represent the entrance of the bacterium in the systemic circulation^[11]. Therefore, intestinal mucosal damage in IBD patients chronically harboring *Listeria* may make them more susceptible to develop Listeriosis during anti-TNF therapy, particularly in case of ingestion of processed meat that increase this risk^[10].

CLINICAL SIGNS

The clinical spectrum of *Listeria* infection includes febrile gastroenteritis, bacteremia, meningitis and meningococcal meningitis, focal infections as septic arthritis, and endocarditis; cutaneous infections, polyserositis and cholecystitis have also been described^[12,13]. Bierhoff *et al*^[14] described 2 cases of Listeria Peritonitis in patients on peritoneal dialysis^[14]. The mortality rate, if the condition is undiagnosed, is high (13-34%)^[15]; in non-immunosuppressed patients, 80% has a central nervous system (CNS) infection and 52% of immunosuppressed patients show septicemia^[12]. Rhomboencephalitis may show with the clinical signs of cerebellar ataxia and it is more frequent with hypervirulent clones of *Listeria*^[3]. Brain Abscess may be present in 10% of all cases of NeuroListeriosis and in 85% of these cases, blood cultures are positive suggesting a bloodstream diffusion^[16]. Al-Harbi *et al*^[16] described the development of brain abscess after Rituximab infusion in a patient with Pemphigus Vulgaris.

LITERATURE DATA

The first description of *Listeria monocytogenes* infection during infliximab treatment had been reported in 2000 by Morelli and Wilson^[9]. A review of the United States Food and Drug Administration’s (FDA) Adverse Events reporting program described 3 patients on infliximab therapy for Crohn’s disease (CD) that developed septicemia and/or meningitis; one of these died^[1]. Aparicio *et al*^[17] stressed the fact that the rate of *Listeria* infection in infliximab-treated rheumatic patients (5 out of 82.000) may be

higher than in CD patients (2 out of 104.500) receiving infliximab therapy; this difference might be correlated to a larger concomitant use of methotrexate in rheumatoid arthritis (RA) patients, the different dosage of infliximab in RA and CD, and a higher age of AR patients^[17]. Dixon *et al*^[18], in the British Society for Rheumatology Biologic Register (BSRBR), described 3 cases of Listeriosis out of 7664 patients treated by anti TNF-alpha agents, with this prevalence being higher compared to Listeriosis’s incidence in the general population, estimated to be 0.7 per 100.000 subjects^[19]. In 2010, the FDA Adverse Event Reporting System identified 92 case of Listeriosis related to infliximab therapy^[20]; 69 patients (75%) showed *Listeria* meningitis and 14 of these (20.3%) also had encephalitis. A mortality rate of 17.4% (16/92 cases) was reported, and 15 out of 16 patients (93.8%) died for meningitis. Three cases of *Listeria* were reported by the BSRBR in 1352-person treated by biologic therapy^[21]; none was reported in patients non receiving biologic agents^[21]. The Spanish BIODABASER found an incidence of serious infections of about 53 cases per 1000 persons-year^[22], and 6 *Listeria* infections were identified. The French RATIO registry reported 4 cases of Listeriosis in patients receiving biologic therapy (etanercept, infliximab, adalimumab)^[23]. The FDA Adverse Event Reporting, in a review of reports in patients treated with infliximab or etanercept from 1998 to 2002, reported 38 cases of Listeriosis^[24]. Subsequently, a more comprehensive literature review from 2004 to 2011 reported 266 cases of *Listeria* infections associated with the use of biologic agents^[25]. Most infections were related to the use of infliximab (77.1%), and the others to the use of etanercept (11.7%), adalimumab (9.8%), rituximab (4.1%), abatecept (0.4%), and golimumab (0.4%). Most patients (47.7%) received biological therapies for rheumatologic diseases, 38% for IBD, 10.5% for miscellaneous indications, and 3.4% for hematological conditions. 73% of all these patients were in concomitant immunosuppressive therapy (56% with Steroids and 31.6% with Methotrexate). The median time of the disease’s onset was 184 days. The mortality rate varied from about 11% (adalimumab) to about 30% (rituximab)^[25].

More recently, a few more case have been described, related to high steroid dosage and also to other biological agents (certulizumab, alemtuzumab)^[26,27].

The importance of an early diagnosis of *Listeria* infection should be stressed, particularly for meningitis due to its high mortality. *Listeria* meningitis may be less frequent in ulcerative colitis because *Listeria* organism are not transferred to the CNS by phagocytosis and are killed extracellularly by antibiotic therapy^[4]. Minami *et al*^[4] described *Listeria* septicemia following colonoscopy, and suggested to consider the prevention of bacteriemic complications in immunosuppressed patients before this procedure. *Listeria* species have been added to the “FDA Boxed Warning” for the entire class of anti TNF-alpha therapies^[28].

TREATMENT

Ampicillin is the first choice drug to treat Listeriosis infection and the Meningitis United Kingdom Guidelines recommend to prescribe ampicillin for all patients with suspected meningitis above the age of 55 years to cover *Listeria*^[20]. At present, *Listeria* resistance to antibiotics of the penicillin family has not been found^[29]. The effectiveness of the penicillin family is due to their high affinity for penicillin-binding protein 3 (PBP3), essential transpeptidase participating in the construction of peptidoglycan, a main constituent of the bacterial cell wall^[30]. Cephalosporins are inactive against *Listeria* because they have only weak affinity for PBP3^[3], even

though this resistance may have more complex pathophysiologic grounds^[31]. Aminoglycosides are also indicated for the treatment of Listeriosis^[24]. The second-line drugs, used particularly in penicillin allergic patients, are trimethoprim/sulphamethoxazole, erythromycin, vancomycin and meropenem^[32]. In immunocompromised patients, the therapy should always be prolonged for more than 2 weeks, due to a high risk of relapse^[28].

CONCLUSIONS

It is very important to recognize that every patient during anti TNF-alpha therapy must be informed about the potential risk to contract *Listeria monocytogenes* infection in case of ingestion of high risk foods, and a list of such foods should be given when prescribing TNF-alpha therapy^[20]. An early diagnosis determined by increased medical sensibilization for this infection could permit a reduction of mortality, especially that due to meningitis and septicemia.

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Peer reviewer: Monowar Aziz