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

INTRODUCTION

The therapeutic use of biological agents such as anti tumor necrosis factor (TNF)-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.

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. Also water tanks contaminated by swallows may be a source of infection 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. Listeriosis is considered a relatively rare infection in adults, and it is regarded as an opportunistic infection affecting principally subjects with malignancy and/ or on immunosuppressive therapy, as well as pregnant women.
newborns and elderly subjects\textsuperscript{[41]. A human disease caused by *Listeria monocytogenes* was described for the first time in 1929 by Nyf€feldt\textsuperscript{[7]}; however, the mechanisms of *Listeria* infection have not been clearly elucidated yet\textsuperscript{[11]. 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\textsuperscript{[41]. 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\textsuperscript{[41]. Soulat et al\textsuperscript{[41]} 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\textsuperscript{[41]} 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\textsuperscript{[41].}

The therapeutical use of anti TNF-alpha agents impairs the effect of endogenous TNF-alpha and it may promote the development of Listeriosis\textsuperscript{[41]}, since *Listeria monocytogenes* DNA has been found in the intestine of inflammatory bowel disease (IBD) patients and in control subjects\textsuperscript{[41]. 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\textsuperscript{[41]}, since it has been suggested that the intestine may represent the entrance of the bacterium in the systemic circulation\textsuperscript{[41]. 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\textsuperscript{[41].}

### CLINICAL SIGNS

The clinical spectrum of *Listeria* infection includes febrile gastroenteritis, bacteremia, meningitis and meningonecephalitis, focal infections as septic arthritis, and endocarditis; cutaneous infections, gastroenteritis, bacteremia, meningitis and meningonecephalitis, high steroid dosage and also to other biological agents (certulizumab, alemtuzumab)\textsuperscript{[21,22]. The FDAdverse Event Reporting, in a review of reports in patients treated with infliximab or etanercept from 1998 to 2002, reported 38 cases of Listeriosis\textsuperscript{[24]. Subsequently, a more comprehensive literature review from 2004 to 2011 reported 266 cases of *Listeria* infections associated with the use of biologic agents\textsuperscript{[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)\textsuperscript{[25].

More recently, a few more case have been described, related to high steroid dosage and also to other biological agents (certulizumab, alemtuzumab)\textsuperscript{[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\textsuperscript{[8]. Minami et al\textsuperscript{[41]} described *Listeria* sepsis following colonoscopy, and suggested to consider the prevention of bactericidal 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\textsuperscript{[21].

### 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\textsuperscript{[41]. At present, *Listeria* resistance to antibiotics of the penicillin family has not been found\textsuperscript{[41]. 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\textsuperscript{[21]. Cephalosporins are inactive against *Listeria* because they have only weak affinity for PBP3, even
though this resistance may have more complex pathophysiologic grounds\(^\text{[31]}\). Aminoglycosides are also indicated for the treatment of Listeriosis\(^\text{[29]}\). The second-line drugs, used particularly in penicillin allergic patients, are trimethoprim/sulphamethoxazole, erythromycin, vancomycin and meropenem\(^\text{[32]}\). In immunocompromised patients, the therapy should always be prolonged for more than 2 weeks, due to a high risk of relapse\(^\text{[31]}\).

**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\(^\text{[20]}\). An early diagnosis determined by increased medical sensibilization for this infection could permit a reduction of mortality, especially that due to meningitis and septicaemia.

**REFERENCES**

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