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Review article

Current status on prevention and treatment of canine leishmaniasis

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ABSTRACT

Canine leishmaniasis (CanL) is a parasite-borne disease mainly induced by *Leishmania infantum* in the Old World and *Leishmania chagasi* (*infantum*) in the New World. CanL is a zoonosis transmitted by the bite of infected Phlebotominae flies that act as vectors. CanL is a very serious disease that usually produces death when remains untreated and can be a focus of transmission to other dogs or humans. Infected dogs and other domestic and wild animals act as reservoirs and are a real threat to uninfected/healthy dogs and humans in endemic areas where the sand flies are present. Prevention of new infections in dogs can help to stop the current increase of the disease in humans, reinforcing the concept of "One Health" approach. The management of CanL is being performed using prophylactic measures in healthy dogs – insecticides impregnated in collars or immunostimulants applied by spot-on devices – and chemotherapy in animals that suffer from the disease. Antimonials as first-line monotherapy have proven efficacy in reducing most of the clinical signs of CanL, but they need to be administered during several days, and no complete parasite clearance is achieved, favouring the presence of relapses among treated dogs. Therefore, new drugs, such as miltefosine, or combinations of this drug or antimonials with allopurinol are in the pipeline of clinical treatment of CanL. Recently, there has been an emergence of protective – prophylactic – and curative – autogenous vaccines – immunotherapy tools to face CanL, whose results are still under study. This review highlights the current use of preventive and eradicative weapons to fight against this disease, which is a scourge for dogs and a continuous threat to human beings.

Contents

Abbreviations: CanL, canine leishmaniasis; VL, visceral leishmaniasis; PK, phamacokinetic; Sb^V, pentavalent antimonials; ROS, reactive oxygen species; BCG, Bacillus Calmette-Guérin; FML, fucose and mannose ligand.

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1. Introduction

Canine leishmaniasis (CanL) is a serious zoonotic disease induced by trypanosomatids from the genus *Leishmania* that affect mostly dogs, which become reservoirs of human visceral leishmaniasis (VL). Due to the domestic life of these animals, dogs become a threat to human beings in endemic aereas where climatic conditions permit the presence of vectors. It is estimated that up to thirty species of the genus *Leishmania* can be responsible for this disease (Dantas-Torres et al., 2012). *Leishmania infantum* has been identified as the main aetiologic agent of CanL in the Old World (Gramiccia and Gradoni, 2005), although other species such as *L. chagasi*, *L. mexicana*, *L. braziliensis*, *L. donovani* or *L. amazonensis* may be included as potential aetiologic agents in countries of the New World (Lainson and Shaw, 2005; Alvar et al., 2004).

CanL is transmitted by arthropods – mostly dipters – that act as disease vectors. Seventy out of approximately 900 *Phlebotominae* sandflies species – depending on the geographical region – are involved in the transmission of infective forms from infected to uninfected animals when feeding on the blood after biting. This vector-borne transmission originates a digenetic life cycle consisting of two different phases: (i) the insect phase comprises free-living promastigotes, which are motile-flagellated forms that colonize the middle gut of the sandfly. When the insect bites a non-infected host, the promastigotes migrate to the insect proboscis and transform into infective metacyclic promastigotes; (ii) the host phase comprises the intracellular amastigote form that colonizes macrophages of the infected vertebrate, thus causing the disease. The amastigote form is round-shaped, non-motile and proliferates inside the parasitophorous vacuole, where host cell lysosomes are fused. *Phlebotomus perniciosus, P. ariasi*, and *P. papatasi* are the sand fly species responsible for CanL leishmaniasis in the Mediterranean Basin, whereas *Lutzomyia longipalpis* and *Lu. chagasi* are some of the incriminated vectors transmitting *L. braziliensis*, *L. chagasi*, *L. panamensis*, *L. peruviana* and *L. amazonensis* in South America (see review by Ready, 2013). All these vectors can transmit the disease after having a bloodmeal on infected dogs despite they are asymptomatic. However, the transmission efficiency of these animals is lower in comparison with ill dogs (Soares et al., 2011). *Leishmania* parasites have been identified in other blood-feeding arthorpods such as ticks or fleas in endemic areas, but their role in epidemiological transmission is not proven (Baneth, 2014). Least but not last, there are other potential ways of transmitting leishmaniasis, such as transplacental (Díaz-Espiñeira and Slappendel, 1997; Boggiatto et al., 2011), organ transplantation (Barsoum, 2004) or blood transfusion (Freitas et al., 2006).

CanL is a severe disease that affects several millions of domestic dogs in countries at both shores of Atlantic Ocean (mainly Europe and South America, but spreading in Africa and Asia as well) and may kill infected dogs when left untreated. It presents several forms that can be typified by their numerous clinical signs, including cutaneous and visceral signs. In general, lesions of leishmaniotic dogs are associated with a pyrogranulomatous inflammatory reaction (Baneth and Aroch, 2008). The most prevalent clinical signs are peripheral lymphadenopathy, weight loss, muscular atrophy, decreased appetite and lethargy (Ciaramella et al., 1997; Koutinas et al., 1999; Baneth et al., 2008). Other symptoms are, dermatological signs (alopecia, papular and nodular dermatitis and furfuraceous dermatitis), onychogryphosis, epistaxis, diarrhea and splenomegaly (Noli and Saridomichelakis, 2014). Renal disease is present with nephritis and glomerulonephritis, and therefore, sick dogs progress from mild proteinuria to nephrotic syndrome and finally chronic renal failure (Koutinas et al., 1999; Marzochi et al., 1985). Eye lesions including keratoconjunctivitis, blepharitis and uveitis are also frequent (Baneth and Aroch, 2008; Freeman, 2010). There is no evidence that thyroid gland alterations or decrease in tyroid hormones occurs during this infection as it happens in other diseases (Saridomichelakis et al., 2013). All these clinical signs appear in varying proportions in symptomatic dogs and every single case does not show them all, although in the vast majority of cases the disease begins with the cutaneous form and evolves towards the visceral one after a variable pre-patency period (Oliva et al., 2006).

L. infantum zymodeme (a group of parasites with the same isozymes) MON1 is the main responsible for CanL in areas of the Mediterranean Sea (Aït-Oudhia et al., 2011), central and southwest Asia (Alam et al., 2009), North and Northwest China (Alam et al., 2014; Wang et al., 2011), sub-Saharan Africa (Hotez and Kamath, 2009) in the Old World and in parts of South America (Kuhls et al., 2011), which supports the hypothesis of a recent importation from south European countries.

The majority of dogs do not develop disease or clinical signs. The prevalence of the disease is around 10% in endemic areas, although it is below 0.4% in East France (Mattin et al., 2014) and over 19% in Greece (Athanasiou et al., 2012). Dogs without clinical signs, but with antibody titter in blood are also found. Seroprevalence ranges between 20% in Southern Spain (Martín-Sánchez et al., 2009) and Balearic Islands (Solano-Gallego et al., 2001), to 40% in Southern Italy (Gramiccia, 2011).

Furthermore, over the past two decades, the disease has spread to Northern territories (Baneth et al., 2008) where it was absent, due to several factors that include changes in the distribution of vectors, tourism with pets to endemic countries (Díaz-Espiñeira and Slappendel, 1997; Teske et al., 2002), and poor control measures (Dujardin, 2006). This high prevalence of *L. infantum* infection in endemic areas where the vector is present, contributes to its dissemination among other dogs (Gramiccia, 2011; Laurenti et al., 2013). A similar scenario can be found in South American countries, where seroprevalence varies from some areas to others depending on diagnostic methods. Nevertheless, prevalence of infected dogs is high and can rise over 60% in some regions of Brazil (Freitas et al., 2010). These variations in infection prevalence rates may be influenced by many other factors, including the accuracy of diagnostic methods, gender, age, breeding, fur length, idiosyncratic genetic