Leishmaniosis in canines: part 1 – treating and controlling infection

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ABSTRACT

Leishmania species are an important cause of infection in both humans and dogs, and continue to provide clinical challenges pertaining to treatment and control.

The combination of meglumine antimoniate and allopurinol is the first line of pharmaceutical treatment. However, the therapy has not fulfilled the promise of achieving complete cure status.

Treatment of canine leishmaniosis (CanL) remains problematic; the optimal regimen is largely unknown and, although most dogs recover clinically after therapy, complete eradication of the parasite is usually not achieved and treated dogs may relapse. CanL is a serious disease in dogs and a reservoir for human infection, so well-tolerated and highly effective treatment modalities free from the limitations associated with therapeutics are urgently needed.

This article provides a critical appraisal of the pros and cons of treatment and prophylactic approaches used for the management of CanL in Europe.

The importance of canine leishmaniosis (CanL) in Europe is growing.

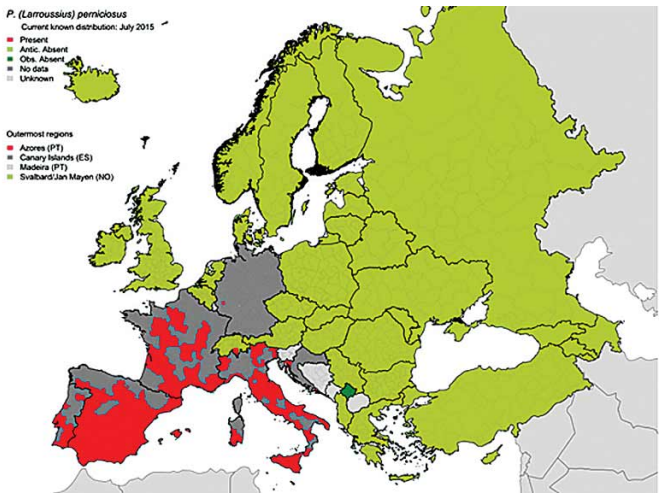

Figure 1. A map showing the geographic distribution of *Phlebotomus perniciosus* sandfly species in Europe at "regional" administrative level (NUTS3). The map is based on published historical data and confirmed data provided by experts from the respective countries. More information at http://tinyurl.com/okgkpm6

This is due to:

- the effects of climatic and environmental changes on the distribution of the sandfly vector of the disease (**Figure 1**)
- increased northwards expansion of the infection from south European endemic regions
- increased travelling of humans with their dogs
- inadequate health control of stray and sheltered dogs, especially in endemic areas
- the difficulty associated with the detection of CanL, due to the long and variable incubation period and polymorphic clinical picture of the disease
- variable clinical response to treatment
- probability of clinical recurrence after treatment
- the requirement of lifelong post-therapy follow-up
- the threat of exotic or new *Leishmania* species

All these challenges make optimal CanL management a difficult task.

Management

The responsibility of veterinary practitioners must be the clinical management of the disease in dogs, which will also reduce parasite transmission since dogs are the main reservoir of infection.

A thorough diagnostic procedure should be established to evaluate infected and sick dogs. The best treatment for sick dogs should then be chosen, bearing in mind the potential risks for resistance development in drugs used in humans.

Clinicians must also focus on eliminating or minimising the incidence of CanL through preventive techniques, parasite clearance and resolution of early lesions resulting from skin inflammatory/allergic response to insect bites. Staging systems and consensus treatment guidelines have been published (Solano-Gallego et al, 2009).

CanL management can be achieved using an integrated approach, including chemotherapeutic agents, vaccine against *Leishmania infantum*, immunoprophylaxis and topical insecticides with a highly repellent effect against sandflies, as well as other means of vector control.

Chemotherapy

Many anti-*Leishmania* chemotherapeutic compounds can reduce the parasitic load.

Treatment with most anti-*Leishmania* compounds can be prolonged and cost may be substantial. Hence, before chemotherapy, veterinarians should inform their clients about the prognosis, costs and the fact the dog perhaps remains infected even when a clinical cure has been achieved.

Also, certain country-specific veterinary public health regulations have to be followed.

Commonly used anti-*Leishmania* drugs are not licensed for the treatment of CanL in the UK, but can be used under the cascade:

- Meglumine antimoniate selectively inhibits the *Leishmania* enzymes required for glycolytic and fatty acid oxidation. It is used alone or in combination with allopurinol. On their own, antimony compounds are rarely successful in completely eradicating the parasite in infected dogs. In contrast, combinational therapy seems to be the most recommended option for treating dogs with confirmed clinical illness because it can yield a longer period of clinical remission than treatment with either drug alone (Noli and Auxilia, 2005). Extreme caution should be exercised in patients with cardiac, hepatic or renal insufficiency.
- Allopurinol (at 15mg/kg orally every 12 hours) is a synthetic isomer of hypoxanthine. It works by slowing the production of uric acid by binding to and inhibiting xanthine oxidase, which subsequently blocks the conversion of hypoxanthine to xanthine and of xanthine to uric acid. In veterinary medicine, allopurinol is used for prophylactic treatment of recurrent uric acid uroliths and hyperuricosuric calcium oxalate uroliths in dogs, especially Dalmatians. In the context of parasitic diseases, allopurinol is used as an alternative treatment for CanL. It has clinical efficacy, but must be used for many months and does not clear the parasite in most dogs at usual doses. Allopurinol is metabolised by *Leishmania* into an inactive form of inosine that is incorporated into the parasite’s RNA, leading to faulty protein and RNA synthesis and inhibition of parasite multiplication. Allopurinol is best used with an antimonial drug as aforementioned.
- Miltefosine was developed as an antineoplastic agent and possesses antiviral and immune-modulatory activity. It can be used alone or with allopurinol to treat CanL; clinical efficacy

improves when used with allopurinol. The exact action mechanism is not completely known, but it is thought it inhibits the penetration of the parasite into macrophages by interacting with glycosomes and glycosylphosphatidylinositol-anchored proteins that are important for the survival of the parasites in the host cells. Also, it inhibits phospholipase, which leads to disruption of the parasite membrane signal transduction and apoptotic death of the parasite. It is contraindicated in pregnant, lactating or breeding animals.

Table 1. Chemotherapeutic protocols applied in canine leishmaniosis (adapted from Solano-Gallego et al, 2009)

Protocol	Drugs and dosages	Main side effects
First line	Meglumine antimoniate (N-methylglucamine antimoniate[a,b]) 75mg/kg to 100mg/kg SID for 4 weeks to 8 weeks SC; plus allopurinol[b] 10mg/kg q12h for at least 6 months to 12 months PO.	● Potential nephrotoxicity and cutaneous abcesses/cellulitis (N-methylglucamine antimoniate). ● Xantine urolithiasis (allopurinol).
Second line	Miltefosinea 2mg/kg SID for 4 weeks PO; plus allopurinol[b] 10mg/kg q12h for at least 6 months to 12 months PO.	● Vomiting, diarrhoea (miltefosine). ● Xantine urolithiasis (allopurinol).
	When an antimonial cannot be used, allopurinol can be used alone[b] 10mg/kg to 20mg/kg q12h for 1 month to 4 months, or longer, PO. If dog has renal insufficiency, allopurinol 5mg/kg twice daily PO.	● Xantine urolithiasis.
Third line	Amphotericin B[c] 0.5mg/kg to 0.8mg/kg IV, SID twice per week for 2 months.	● Nephrotoxicity.
	Liposomal amphotericin B[c] 3mg/kg SID for 5 consecutive days IV.	● Transient nephrotoxicity.
	Metronidazole 25mg/kg SID; plus spiramycin 150,000U SID for 3 months PO.	● Not described.
	Marbofloxacin 2mg/kg SID for 1 month PO.	● Not described.

[a] Registered for veterinary use in Europe. [b] Allopurinol is used under the cascade. [c] First line drug for human visceral leishmaniasis in Europe; not recommended by World Health Organization for veterinary use, to avoid drug parasite resistance.

Table 1. Chemotherapeutic protocols applied in canine leishmaniosis (adapted from Solano-Gallego et al, 2009).

Clinicians should be aware of the benefits of combination therapy versus monotherapy for CanL patients. It is unlikely one single drug is able to satisfy all the needs and expectations for CanL management. The primary reasons for combination therapy are to prevent resistance development, improve outcomes, provide synergy and ensure sufficient anti-Leishmania coverage should the parasite resist the drug that would have been used as single therapy.

More details about the doses and side effects of these drugs, and others used to treat clinical cases of CanL, are provided in **Table 1**.

Post-treatment monitoring and prognosis

Infected dogs may remain disease carriers despite treatment. This poses a challenge to owners, veterinarians and local public health and environmental agencies in endemic areas where sandfly vectors are found. Therefore, follow-up and monitoring of clinical and laboratory parameters of treated dogs are essential for proper case management and to prevent infection transmission.

Meglumine antimoniate is the main antimonial used for CanL treatment and has been the primary drug for treatment of CanL and human leishmaniasis. However, it is important to note, in endemic areas, reinfection and relapses occur once therapy has been discontinued and complete recovery

is rare, even after long-term treatment.

Deterioration of kidney function may also continue during allopurinol therapy, despite the resolution of dermal lesions and general improvement on the clinical condition.

For seriously ill dogs, especially those in severe renal failure secondary to *Leishmania* infection, it may be necessary to restore fluid and acid-base balances and to manage the complications of uraemia and protein-losing nephropathy before anti-*Leishmania* drugs are administered.

CanL prognosis depends on the severity of injury to the dog's systems at the time of diagnosis and the dog's individual response and rate of clinical deterioration. In dogs that have not reached a progressive state or renal failure, treatment frequently significantly improves dermal and visceral signs of the disease. In some cases, parasite-specific cell-mediated immunity, absent before therapy, can be regained after drug administration, but may deteriorate again during a clinical relapse.

Vaccination

A number of *Leishmania* antigens have been identified as potential vaccine candidates; however, very few have been tested in clinical trials and only three canine vaccines have been registered.

The first vaccine, Leishmune, was licensed in Brazil in 2003 and is composed of the promastigote antigen (fucose mannose ligand) and the adjuvant saponin. A second vaccine, Leish-Tec, a recombinant A2 antigen of *Leishmania* amastigotes adjuvanted by saponin, has been licensed since 2008.

In 2011, CaniLeish, a formulation related to culture supernatant of *L infantum promastigotes*, composed of 54 kiloDaltons secreted-excreted antigens of *L infantum* (LiESP/QA-21), was the first vaccine licensed for use in Europe.

Vaccination is designed to induce a strong, protective, T helper 1-dominated, cellular anti-*Leishmania* immune response within three to four weeks of administration (Palatnik-de-Sousa, 2012). This vaccine has shown to significantly reduce the number of actively infected animals and reduce the development of clinical disease (Bongiorno et al, 2013; Martin et al, 2014; Oliva et al, 2014). CaniLeish is restricted to seronegative dogs younger than six months and induces anti-*Leishmania* antibodies detectable by the immunofluorescence antibody test.

Suspected clinical leishmaniosis in vaccinated dogs requires the use of parasitological methods. A rapid anti-kinesin qualitative test claims to discriminate between antibodies induced by natural infection and those due to vaccination. Vaccine history is crucial for interpreting results of *Leishmania* immunological tests in dogs in Europe.

Overall, CaniLeish vaccination appears to have sufficient efficacy to justify ongoing vaccination programmes in areas where CanL is highly endemic. However, like all vaccinations, efficacy is not 100 per cent and vaccine does not prevent contact with the vector, thus a history of vaccination does not eliminate the need to consider the use of immune-prophylactic and vector control measures.

Immune boosters

A hyperprolactinaemic immunomodulatory domperidone-based oral suspension is used in parts of Europe for preventive and therapeutic treatment against CanL (Gomez-Ochoa et al, 2009).

Domperidone, a gastric prokinetic and anti-emetic drug, acts as a dopamine receptor D2 antagonist resulting in the release of serotonin, which, in turn, stimulates prolactin production. Prolactin has a central role in the immune reaction, although its mechanism of action is largely unknown.

Domperidone enhances innate defence mechanisms activating phagocytic cells and potentiates the intracellular killing of the parasites. It has been found a 30-day course of therapy has an early stimulatory effect that persists for one month after the end of administration, significantly reducing the risk of developing clinical CanL in areas with high prevalence of the disease (Sabaté et al, 2014).

Canine leishmaniosis: part 2 – keeping sandflies at bay

References

- Bongiorno G, Paparcone R, Foglia Manzillo V et al (2013). Vaccination with LiESP/QA-21 (CaniLeish) reduces the intensity of infection in *Phlebotomus perniciosus* fed on *Leishmania infantum* infected dogs – a preliminary xenodiagnosis study, *Vet Parasitol* **197**(3-4): 691-695.
- Gomez-Ochoa P, Castillo JA, Gascón M et al (2009). Use of domperidone in the treatment of canine visceral leishmaniasis: a clinical trial, *Vet J* **179**(2): 259-263.
- Martin V, Vouldoukis I, Moreno J et al (2014). The protective immune response produced in dogs after primary vaccination with the LiESP/QA-21 vaccine (CaniLeish) remains effective against an experimental challenge one year later, *Vet Res* **45**: 69.
- Noli C and Auxilia ST (2005). Treatment of canine old world visceral leishmaniasis: a systematic review, *Vet Dermatol* **16**(4): 213-232.
- Oliva G, Nieto J, Foglia Manzillo V et al (2014). A randomised, double-blind, controlled efficacy trial of the LiESP/QA-21 vaccine in naïve dogs exposed to two *Leishmania infantum* transmission seasons, *PLoS Negl Trop Dis* **8**(10): e3213.
- Palatnik-de-Sousa CB (2012). Vaccines for canine leishmaniasis, *Front Immunol* **3**: 69.
- Sabaté D, Llinás J, Homedes J et al (2014). A single-centre, open-label, controlled, randomized clinical trial to assess the preventive efficacy of a domperidone-based

treatment programme against clinical canine leishmaniasis in a high prevalence area, *Prev Vet Med* **115**(1-2): 56-63.
- Solano-Gallego L, Koutinas A, Miró G et al (2009). Directions for the diagnosis, clinical staging, treatment and prevention of canine leishmaniosis, *Vet Parasitol* **165**(1-2): 1-18.