IMUNOTERAPIA COM VACINA LEISH-TEC® NA LEISHMANIOSE VISCERAL CANINA

TRATAMENTO DA LEISHMANIOSE VISCERAL CANINA

J Vet Intern Med 1999;13:413–415

Combination Allopurinol and Antimony Treatment versus Antimony Alone and Allopurinol Alone in the Treatment of Canine Leishmaniasis (96 Cases)

Philippe Denerolle and Gilles Bourdoiseau

The aim of the present study was to evaluate the long-term clinical outcome for dogs with leishmaniasis that were treated with 3 different protocols: combined treatment with antimony and allopurinol, antimony alone, or allopurinol alone. Ninety-six dogs included in this study were determined to have leishmaniasis on the basis of (1) clinical features, (2) identification of the parasite in smears of lymph node, bone marrow aspirates, or skin biopsies, and (3) specific immunofluorescent assay. Three groups of dogs were defined: 45 dogs (group 1) were treated with antimony (100 mg/kg SC q24h) given concurrently for 1 month with allopurinol (15 mg/kg PO q12h), and then allopurinol alone for 8 months at the same dosage; 40 dogs (group 2) were treated with antimony alone according to the manufacturer's instructions (200 mg/kg SC q24h at 2-day intervals for 3–6 months); and 11 dogs (group 3) were treated with allopurinol alone (15 mg/kg PO q12h for 1–20 months). Information concerning signalment, history, physical examination findings, serologic testing and number of dogs becoming seronegative, outcome for each treated dog (clinical cure versus failure), and long-term survival were recorded. The numbers of the clinical cures versus failu[illegible] among the 3 groups ($\chi^2 = 17.77$, $P < .001$), between groups 1 and 2 ($\chi^2 = 8.02$, $P < .01$), betwee[illegible] $P < .01$), and between groups 1 and 3 ($\chi^2 = 16.52$, $P < .001$). No significant difference between the type of failure (relapse or death), serologic test results, and number of survival years ($\chi^2 = 2.79$ present study indicate that antimony in combination with allopurinol produces better results than [illegible] alone for the treatment of the canine leishmaniasis. With combination treatment, duration of treatm and long-term administration of allopurinol is well tolerated.

Key words: Dogs; *Leishmania infantum*; Protozoal disease; Therapy.

Veterinary Dermatology

DOI: 10.1111/j.1365-3164.2009.00824.x

Multicentric, controlled clinical study to evaluate effectiveness and safety of miltefosine and allopurinol for canine leishmaniosis

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allopurinol, offers a safe, convenient and effective alternative treatment option for canine leishmaniosis compared to the reference therapy.

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Introduction

In the Mediterranean basin, human visceral leishmaniosis and canine leishmaniosis (CanL) are endemic. Both diseases are serious and can be fatal if untreated. CanL

TRATAMENTO DA LEISHMANIOSE VISCERAL CANINA

FÁRMACOS CONTRA LEISHMANIOSE VISCERAL CANINA (UTILIZAÇÃO MUNDIAL)

Antimoniais – antimoniato de n-metil Glucamina

Estibogluconato de sódio –Pentostam 30 a 50 mg/kg/SID

Anfotericina B / Anfotericina lipossomal

Miltefosina 2 mg/kg/SID - 28 dias

Cetoconazol (07-25 mg/kg/SID - 90 dias)

Aminosidina

Alopurinol 20mg/kg/BID ou TID- mínimo de 2 anos

Metronidazol (25mg/kg) + espiramicina (150.000UI/kg) - SID

Quinolonas (Marbofloxacina)

TRATAMENTO DA LEISHMANIOSE VISCERAL CANINA

FÁRMACOS CONTRA LEISHMANIOSE VISCERAL CANINA (UTILIZAÇÃO MUNDIAL)

- IMUNOMODULADORES

  PREDNISOLONA 1,0 A 0,5 MG/KG/SID POR 30 DIAS

- IMUNOESTIMULANTES

  LEVAMISOLE (0,5-2mg/kg cada 2 dias)

  INTERFERON (10UI/KG/SID)

  DOMPERIDONA 0,5 A 1,0 MG/KG/SID OU BID – 30 A 60 DIAS

Vacina

Imunoterapia

Aliada na terapêtica contra a LVC

1.
Imunoterapia na LVC

ESTUDOS

Imunoterapia com a vacina Leishmune®

Vaccine 28 (2010) 597–603

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Immunotherapy with the saponin enriched-Leishmune® vaccine *versus* immunochemotherapy in dogs with natural canine visceral leishmaniasis

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ABSTRACT

Leishmune®, the first licensed vaccine for prophylaxis against canine visceral leishmaniasis (CVL) and is also immunotherapeutic when used with double saponin adjuvant concentration. The Leishmune® therapeutic vaccine was assessed for immunotherapy (IT) in 31 infected dogs and for immunochemotherapy (ICT) in combination with allopurinol or amphotericinB/allopurinol, in 35 dogs. Compared to infected untreated control dogs, at month 3, both treatments increased the proportion of dogs showing intradermal response to *Leishmania* antigen to a similar extent (from 8 to 67%, in the IT and to 76%, in the ICT groups), and conversely reduced from 100 to 38% (IT) and to 18% (ICT) the proportion of symptomatic cases, from 54 to 12% (IT) and to 15% (ICT) the proportion of parasite evidence in lymph nodes and from 48 to 19% (IT) and 12% (ICT) the proportion of deaths, indicating that the immunotherapy with enriched-Leishmune® vaccine promotes the control of the clinical and parasitological signs of CVL rendering most

Imunoterapia

.....Saponinas são glicosídeos naturais de esteroides ou triterpenos que exibem atividades biológicas, como de estimular a resposta imune Th1, quanto a produção e linfócitos T citotóxicos.....

Vacina Leish-Tec®

Vaccine 26 (2008) 5888–5895

Contents lists available at ScienceDirect

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Protective immunity against challenge with *Leishmania* (*Leishmania*) *chagasi* in beagle dogs vaccinated with recombinant A2 protein

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ABSTRACT

In this study, we investigated in dogs the immunogenicity and protective immunity against *Leishmania*

Imunoterapia com vacina Leish-Tec®

Worldleish 5
Fifth World Congress on Leishmaniasis

EVALUATION OF IMMUNOTHERAPY ASSESSMENT LEISH-TEC® ASSOCIATED WITH ALLOPURINOL IN DOGS NATURALLY INFECTED BY Leishmania infantum - PRELIMINARY RESULTS.

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Sixteen dogs of different breeds and ages naturally infected by Leishmania infantum were selected. The infection in these animals was confirmed by indirect immunofluorescence (IFI), PCR and parasitological examination. Nine animals were symptomatic and seven asymptomatic; five of them showed anemia and 11 had normal hematocrit; fraction Albumin / Globulin (A/G) was below 0.6 mg/dL in five dogs and normal in 11; the search of parasites on the skin of the apex of the inner ear via the method of immunohistochemistry (IHC) was positive in 6 animals and negative in 10. In full dilution of serum antibodies by IFI, 5 animals had titers of 1:40 to 1:320, 10 of 1:640 to 1:5120 and one showed the title of 1:10240. The animals were treated with Leish-Tec® using double dose, in three applications, with intervals of 21 days reapplying every six months. They were also treated with oral allopurinol, 10 to 20 mg/kg twice a day during the entire period. The evaluation of the animals after 6 months of treatment revealed that 13 animals were asymptomatic with normal hematocrit, and the fraction A/G in 12 was normal. Out of the 16 evaluated animals by IHC, amastigotes were found only in one. Serological evaluation showed seroconversion in 8 animals and 7 had titles of 1:320. Conclusion: We can conclude that immunotherapy with Leish-Tech® associated with allopurinol can induce clinical and laboratorial improvements in dogs with visceral leishmaniasis, as long as the reduction of cutaneous parasitism, and the reduction of the anti-L. infantum titers. Becoming, therefore, an option of treatment in the treatment protocol of the disease in dogs.

Imunoterapia com vacina Leish-Tec®

C1768 CLINICAL MANAGEMENT OF SOROPOSITIVE DOGS FOR VISCERAL LEISHMANIASIS, ASYMPTOMATICS AND WITH NO INFECTING POTENTIAL FOR SAND FLIES.

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1 Background

Canine Visceral Leishmaniasis (CVL) is a chronic and fatal disease, when untreated. It is caused by a digenetic protozoan named *Leishmania infantum*, which also infects humans and other animal species. Its transmission occurs by the bite of infected dipteran sandflies insects of the species *Lutzomyia longipalpis*. The dog is the main domestic reservoir of *L. infantum*, but the diagnosis of infection is often difficult, either due to the low anti-*Leishmania* antibodies titers, the absence of parasitic forms in parasitological and molecular tests, absence of physical signs and normality of the complementary tests such as the complete blood count, renal and hepatic profile and serum protein levels. Animals in these conditions are not classified as infected but rather as suspects and do not have a protocol of therapeutic management or established follow-up

2 Methods

In order to monitor suspected CVL animals, thirty-two dogs, of different breeds, varied ages and both sexes, with positive serological results, IFAT and/or ELISA, were followed for one year, but with low titers, parasitological and/or molecular tests negatives, absence of physical signs and alterations in the complementary tests classified as suspected (Stage I) of CVL.

3 Results

Of these thirty-two animals, in the first evaluation, 26/32 were ELISA reagents and in IFAT, 17/32 had titles 1:40, 13/32 1:80 and 2/32 1: 160. All dogs were submitted to immunotherapy, based on the application of the *L. infantum* A2 antigen associated with 1 mg of saponin as adjuvant (two vials of the Leish-TecR vaccine), in three administrations with 21-day intervals and one administration every six months. These animals were evaluated one year later and 13/32 were maintained ELISA reagents; in IFAT, 21/32 were negative, 3/32 had titles 1:40, 7/32 1:80 and 1/32 1: 160. The physical pattern remained asymptomatic, parasitological and/or molecular exams continued negative and the complementary tests remained within the normality

2.
Imunoterapia na LVC

COMO UTILIZAR

Imunoterapia com vacina Leish-Tec®

DOSE DUPLA DA VACINA COM INTERVALO DE 21 DIAS

TRÊS APLICAÇÕES

REPETIR A DOSE DUPLA A CADA SEIS MESES

3.
Imunoterapia na LVC

QUANDO UTILIZAR

Imunoterapia com vacina Leish-Tec®

ESTADIAMENTO CLÍNICO DA ENFERMIDADE

Solano-Gallego et al. Parasites & Vectors 2011, 4:86
http://www.parasitesandvectors.com/content/4/1/86

Parasites & Vectors

REVIEW Open Access

LeishVet guidelines for the practical management of canine leishmaniosis

Laia Solano-Gallego[1*], Guadalupe Miró[2], Alek Koutinas[3], Luis Cardoso[4], Maria Grazia Pennisi[5], Luis Ferrer[6], Patrick Bourdeau[7], Gaetano Oliva[8] and Gad Baneth[9]

Table 4 Clinical staging of canine leishmaniosis based on serological status, clinical signs, laboratory findings, and type of therapy and prognosis for each stage [27]

Clinical stages	Serology *	Clinical signs	Laboratory findings	Therapy	Prognosis
Stage I Mild disease	Negative to low positive antibody levels	Dogs with mild clinical signs such as peripheral lymphadenomegaly, or papular dermatitis	Usually no clinicopathological abnormalities observed Normal renal profile: creatinine < 1.4 mg/dl; non-proteinuric: UPC < 0.5	Scientific neglect/allopurinol or meglumine antimoniate or miltefosine/allopurinol + meglumine antimoniate or allopurinol + miltefosine**	Good
Stage II Moderate disease	Low to high positive antibody levels	Dogs, which apart from the signs listed in stage I, may present: diffuse or symmetrical cutaneous lesions such as exfoliative dermatitis/onychogryphosis, ulcerations (planum nasale, footpads, bony prominences, mucocutaneous junctions), anorexia, weight loss, fever, and epistaxis	Clinicopathological abnormalities such as mild non-regenerative anemia, hyperglobulinemia, hypoalbuminemia, serum hyperviscosity syndrome **Substages** a) Normal renal profile: creatinine < 1.4 mg/dl; non-proteinuric: UPC < 0.5 b) Creatinine <1.4 mg/dl; UPC = 0.5-1	Allopurinol + meglumine antimoniate or allopurinol+ miltefosine	Good to guarded
Stage III Severe disease	Medium to high positive antibody levels	Dogs, which apart from the signs listed in stages I and II, may present signs originating from immune-complex lesions: vasculitis, arthritis, uveitis and glomerulonephritis.	Clinicopathological abnormalities listed in stage II Chronic kidney disease (CKD) IRIS stage I with UPC > 1 or stage II (creatinine 1.4-2 mg/dl) [79]	Allopurinol + meglumine antimoniate or allopurinol + miltefosine Follow IRIS guidelines for CKD [80]	Guarded to poor
Stage IV Very severe disease	Medium to high positive antibody levels	Dogs with clinical signs listed in stage III. Pulmonary thromboembolism, or nephrotic syndrome and end stage renal disease	Clinicopathological abnormalities listed in stage II CKD IRIS stage III (creatinine 2-5 mg/dl) and stage IV (creatinine > 5 mg/dl) [79] Nephrotic syndrome: marked proteinuria UPC > 5	Allopurinol (alone) Follow IRIS guidelines for CKD [80]	Poor

*Dogs with negative to medium positive antibody levels should be confirmed as infected by other diagnostic techniques such as cytology, histology, immunohistochemistry or PCR. High levels of antibodies, defined as a 3-4 fold elevation above the cut off level of a well established reference laboratory, are conclusive of a diagnosis of CanL. **Dogs in stage I (mild disease) are likely to require less prolonged treatment with one or two combined drugs or alternatively monitoring with no treatment. However, there is limited information on dogs in this stage and, therefore, treatment options remain to be defined.

Imunoterapia com vacina Leish-Tec®

ESTADIAMENTO CLÍNICO DA ENFERMIDADE

BRASILEISH

Tabela 3

ESTADIAMENTO CLÍNICO, MANEJO E TRATAMENTO DA LEISHMANIOSE CANINA BASEADO NA SOROLOGIA, SINAIS CLÍNICOS E ACHADOS LABORATORIAIS. A ANÁLISE E TERAPÊUTICA RECOMENDADA SE BASEIA EM PROTOCOLOS TERAPÊUTICOS ATUALMENTE DISPONÍVEIS NO BRASIL (adaptado de Solano-Gallego et al., 2011)

Estádios clínicos	Sorologia [1]	Sinais clínicos	Resultados laboratoriais	Terapia[2]	Prognóstico
ESTÁDIO I Sem doença	Positiva com níveis de anticorpos baixos a médios / parasitológico negativo	Ausentes	Sem alterações	Imunoterapia[3] + imunomodulação[4]	Bom
ESTÁDIO II Sem Doença / Doença leve	Negativa ou positiva com níveis de anticorpos baixos a médios / parasitológico positivo	Sinais clínicos ausentes a leves, como linfadenopatia periférica, dermatite papular, emagrecimento discreto	Geralmente sem alterações. Perfil renal normal	Imunoterapia[3] + imunomodulação[4] + alopurinol + miltefosina	Bom
ESTÁDIO III Doença moderada	Positiva com níveis de anticorpos baixos a altos / parasitológico positivo	Sinais do Estádio II, além de outros como lesões cutâneas difusas ou simétricas, onicogrifose, ulcerações, anorexia e emagrecimento	Anemia não regenerativa leve, hipergamaglobulinemia, hipoalbuminemia, síndrome da hiperviscosidade do soro (proteínas totais >12 g/dl) oriundos da formação de imunocomplexos, tais como uveíte e glomerulonefrite. **Subestádios** a) Perfil renal normal (Creatinina <1,4 mg/dl; RPC <0,5 b) Creatinina <1,4 mg/dl; RPC = 0,5-1	Imunoterapia[3] + imunomodulação[4] + alopurinol + miltefosina Seguir as diretrizes da IRIS para o manejo da nefropatia e controle PSS	Bom a reservado
ESTÁDIO IV Doença grave	Positiva com níveis de anticorpos médios a altos / parasitológico positivo	Sinais do Estádio IV, além de tromboembolismo pulmonar ou síndrome nefrótica e doença renal em estádio final.	Alterações do Estádio III, além de DRC no Estádio 1 (RPC >1) ou 2 (creatinina 1,4-2 mg/dl) da IRIS	Imunoterapia[3] + imunomodulação[4] + alopurinol + miltefosina Seguir as diretrizes da IRIS para o manejo da DRC e controle PSS	Reservado a pobre
ESTÁDIO V Doença muito grave	Positiva com níveis de anticorpos médios a altos / parasitológico positivo	Sinais dos Estádio IV, além de tromboembolismo pulmonar ou síndrome nefrótica e doença renal em estádio final	Alterações do Estádio IV, além de DRC no estádio III (creatinina 2,1-5 mg/dl) e IV (creatinina > 5 mg/dl) da IRIS, ou síndrome nefrótica (marcada proteinúria com RPC >5)	Imunoterapia[3] + imunomodulação[4]+ alopurinol + miltefosina Seguir as diretrizes da IRIS para o manejo da DRC e controle PSS	Pobre

Abreviações: RIFI (reação de imunofluorescência indireta); DRC (doença renal crônica); IRIS (International Renal Interest Society); PSS (pressão sistêmica sanguínea); RPC (razão proteína-creatinina urinárias).

1Em cães soronegativos ou com níveis de anticorpos baixos ou médios, a infecção deve ser confirmada por meio de citologia, histologia, imuno-histoquímica e/ou PCR. Níveis altos de anticorpos (aumento de 3-4 vezes acima do ponto de corte ou cut-off pré-estabelecido de um laboratório de referência) são conclusivos para o diagnóstico da LCan (Solano-Gallego et al., 2011; Ribeiro et al., 2013).

2Monitorar a cada 4 a 6 meses com exames sorológicos, paratsitológicos e/ou moleculares, exames gerais para estadiamento e revisão de tratamento (Ribeiro, 2016; Leishvet, 2018).

3Imunoterapia com a vacina LeishTec: um frasco aos 0, 14 e 28 dias em animais infectados (Toepp et al., 2018) ou dois frascos nos dias 0, 21 e 42, em monoterapia ou associada ao alopurinol, com reforços semestrais (Ribeiro et al., 2013, 2017).

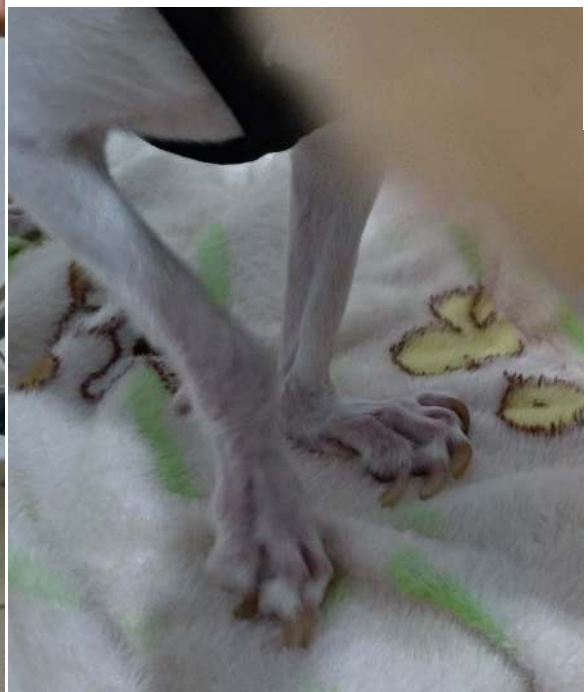
4Imunomodulação com domperidona: 0,5-1 mg/kg duas vezes ao dia por 30 dias (Gómez-Ochoa et al., 2009).

Folha vitória

ROTINA

- Estágio I do estadiamento clínico isolada ou associada com COLEIRA, PIPETA, DOMPERIDONA, ALOPURINOL
- Associada a outros fármacos na terapia contra a LVC independente do estadiamento
- Pacientes com estágios avançados de doenças renais e hepáticas
- Manter polarizada a resposta Th1
- Restrição a manutenção do uso do alopurinol
- Novos estudos

Obrigado



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