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LEISHMANIOSI CANINA

New Insights into the Treatment of Leishmaniasis

Eric Zini

Snow meeting, 14 March 2009

Few drugs available for dogs

- ✓ Initially developed to treat human leishmaniasis, later adopted in dogs
- ✓ None eradicates infection
- ✓ Discrepancy between *“in vitro”* and *“in vivo”* activity



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Proposal

- ✓ Treatment scheme to use in the majority of cases
- ✓ May be modified according to single cases
- ✓ Does not include supportive treatments



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Criteria to review the literature

PubMed (www.ncbi.nlm.nih.gov/pubmed/):

(dog* OR canine) AND (drug OR treat* OR therap* OR efficac* OR effect* OR action* OR activit* OR against OR versus) AND (leishm* OR antileishm*) NOT vaccin*



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initially 90 papers

30 studies excluded because not pertaining therapy

60 papers reviewed

Major limits of the literature:

- ✓ Unblinded trials
- ✓ Lack of controls
- ✓ Small # of enrolled dogs
- ✓ Heterogeneous groups
- ✓ Variable diagnostic and clinical classification criteria
- ✓ Variable definition of clinical/parasitological cure
- ✓ Variable *follow-up*
- ✓ Variable drug doses and treatment duration



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- ✓ Variable definition of clinical/parasitological cure
- ✓ Variable *follow-up* (>6 months: 22)
- ✓ Variable drug doses and treatment duration

In addition...

In many the primary aim is to address issues regarding:

- ✓ Diagnosis / Parasitology
- ✓ Pharmacology
- ✓ Immunology
- ✓ Pathogenesis



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Drugs studied:

- ✓ Meglumine Antimoniate
- ✓ Allopurinol
> 5 references
- ✓ Amphotericin B (classic or liposome-encapsulated)
- ✓ Aminosidine
3-4 references
- ✓ Pentamidine
- ✓ Metronidazole / Spiramycin
- ✓ Enrofloxacin, Marbofloxacin
- ✓ Domperidone
1 reference

Miltefosine

New in dogs, since 2008



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Meglumine Antimoniate

- ✓ Inhibition of *Leishmania* glycolysis and fatty acid oxidation
- ✓ In dogs, 80-95% renal excretion within 6-9 h
- ✓ Clinical improvement in all studies, within 2-8 weeks
- ✓ ↓parasitic load and antibody titer
- ✓ Pain and swelling at injection site, diarrhea and anorexia
- ✓ Resistant strains if more courses

Literature: 34 studies

Allopurinol

- ✓ In *Leishmania* amastigotes allopurinol is transformed in 4APP, which is toxic
- ✓ Better clinical improvement if with Meglumine Antimoniate
- ✓ ↓deterioration of renal function in proteinuric dogs
- ✓ Xanthinuria

Literature: 19 studies

Amphotericin B

- ✓ Impairment of *Leishmania* membrane sterols
- ✓ ↓nephrotoxicity if liposomal
- ✓ Use in dogs discouraged by the WHO

Aminosidine

- ✓ Ribosomal dissociation
- ✓ Better clinical improvement if with Meglumine Antimoniate
- ✓ Renal and vestibular toxicity

Literature: 3 and 4 studies, respectively

Reference Protocol of Therapy

Meglumine Antimoniate

100 mg/kg q24h, SC, for 4 weeks

+

Allopurinol

10 mg/kg q12h, PO, for at least 6 months



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Who to treat?



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Approach to clinical classification

Stage A: EXPOSURE or SUBPATENT INFECTION

- ✓ Negative cyto-histologic and PCR findings
- ✓ “Low-titer” positive serology
- ✓ Clinically healthy or other disease
- ✓ Dogs living or lived during one/more transmission seasons in a territory with *Leishmania* vectors



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Approach to clinical classification

Stage B: PATENT INFECTION

- ✓ Parasites confirmed with direct methods
- ✓ “Low-titer” positive serology
- ✓ Clinically healthy or other disease
- ✓ In endemic areas, positive findings by skin or blood PCR in the absence of lesions and during the infection transmission period may not indicate infection (promastigote DNA)



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Approach to clinical classification

Stage C: DISEASE

- ✓ Infected dogs, showing one/more clinical signs or laboratory alterations compatible with leishmaniasis
- ✓ “High-titer” (or “low-titer”) positive serology



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Approach to clinical classification

Stage D: SEVERE DISEASE

- ✓ Diseased dogs with a severe clinical picture, including:
 - i. unresponsiveness to repeated drug treatments
 - ii. chronic renal failure
 - iii. concurrent problems related or not to leishmaniasis requiring immunosuppression
 - iv. severe concomitant disorders



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Stage	Definition	Description
A	Exposure or Subpatent Infection	NOT TO TREAT

Stage	Definition	Description
B	Patent Infection	NOT TO TREAT <hr/> TREAT

Stage	Definition	Description
C	Disease	
D	Severe Disease	TREAT

Using the Reference Protocol of Therapy...



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Dogs in Stage C (disease):

- Clinical recovery lasting approximately 1 year
- Side effects of least importance
- Consistent reduction of parasitic burden (some months)
- ↓ transmission risk for phlebotomine sandflies



Dogs in Stage D (severe disease):

- Chances to improve are moderate-good
- Prognosis related to concurrent organ dysfunction
- Necessary to provide supportive therapy (e.g., KCS)



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**What's next if the dog does
not respond?**

**Re-assess and consider
concurrent disorders**



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Rationale for using Alternative Protocols

- Dog does not respond (or has prompt relapse)
- Limited owner's compliance
- Intolerance / Side effects



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Alternative Protocols

- Monotherapy with Allopurinol
(less efficient and slower than with Meglumine Antimoniate)
- Amphotericin B and Aminosidine
(possible nephrotoxicity)
- Metronidazole / Spiramycin
- Others



Monitoring and Re-start Treatment Dogs in Stage C (disease)

**If physical exam and blood work do not suggest
the need of supportive therapy,
the following scheme is proposed**



After Meglumine Antimoniate...

- ✓ If dog is normal or improved:
 - every 6 months assess antibody titer, cytology, and qPCR from lymph node or bone marrow (not fully standardized in several labs)
- ✓ If no improvement, the dog is a “non responder”:
 - concurrent disorders?
 - alternative protocols?



Figura 3: Struttura chimica della Miltefosina (esadecilfosfolina)



Miltefosine

- ✓ Phospholipid analogue with anti-cancer activity
 - ✓ Disturbs *Leishmania* signalling pathways and cell membrane synthesis, leading to apoptosis
- ↓
- Leishmanicidal drug
- ✓ Registered for visceral and cutaneous human leishmaniasis
 - ✓ Only effective oral treatment in humans

(Soto et al., Trans R Soc Trop Med Hyg 2006)

Figura 3: Struttura chimica della Miltefosina (esadecilfosfolina)



Miltefosine

- ✓ In dogs:
 - After oral administration 94% bioavailability
 - Max concentration between 4-48 hours
 - Long half-life: 6.3 days, leading to accumulation
 - Side effects: nausea, vomiting, diarrhea
- ✓ Registered for canine leishmaniasis in France, Italy, Greece, Portugal
- ✓ Suggested dose: 2 mg/kg, q24h, for 28 days

Clinical studies in dogs

- ✓ Miltefosine (2 mg/kg, q24h) for 28 days + Allopurinol (10 mg/kg, q24h) for 1 year
- ✓ # of dogs 28
 - Findings:
 - 2 dogs had ↓ PCV and WBC after 7 days of therapy
 - 2 dogs died of renal failure within 5 days
 - 24 dogs completed the study (4 dogs relapsed)
 - ↓ clinical score at 1 mo, until the end
 - ↓ parasitic load (lymph node qPCR) at 1 mo, until the end

(Manna et al., Vet J 2008)

Clinical studies in dogs

- ✓ Miltefosine (2 mg/kg, q24h) vs. Meglumine Antimoniate (100 mg/kg, q24h) for 28 days
- ✓ # of dogs 44 vs. 36
 - 14 days post-therapy:
 - Nausea and vomiting in < 20% of dogs, in both groups
 - Clinical score equally improved
 - % of negative bone marrow smears equal
 - % of dogs with azotemia ↑ with Antimoniate (10.8 vs. 0%)

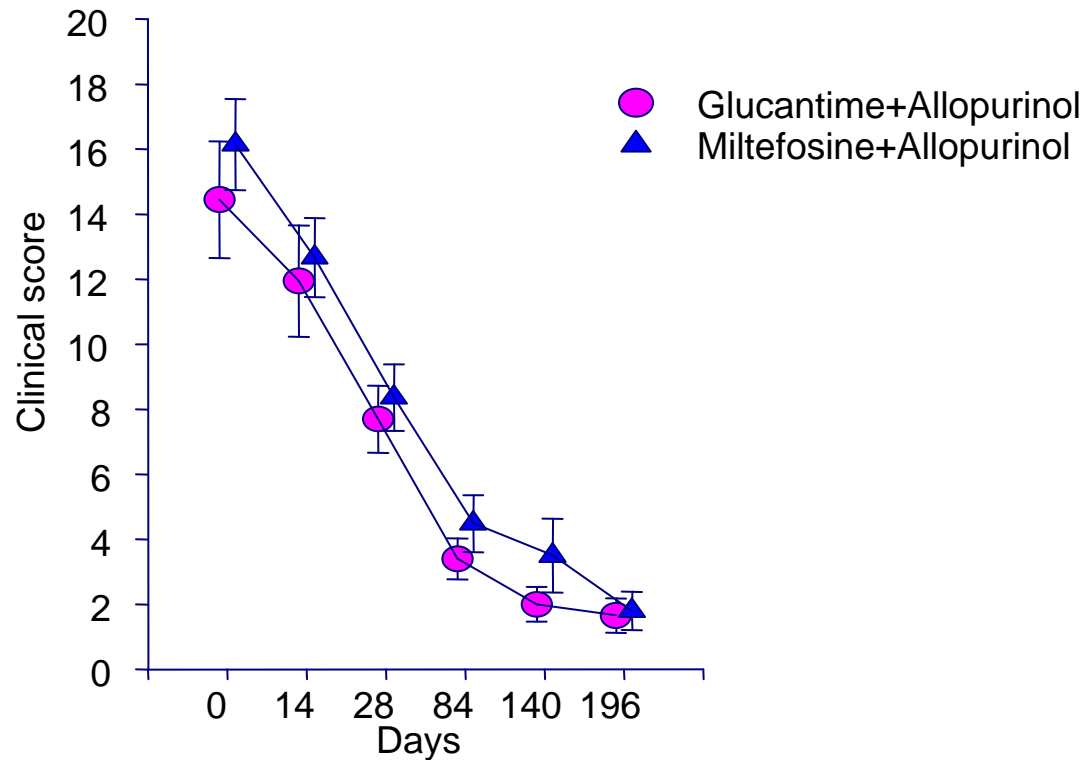
(Mateo et al., Parasitol Res 2009)

Clinical studies in dogs

- ✓ Miltefosine (2 mg/kg, q24h) vs. Meglumine Antimoniate (50 mg/kg, q12h) for 28 days, + Allopurinol (10 mg/kg, q12h) for 7 months
- ✓ # of dogs 37 vs. 36
 - Findings:
 - No side effects (clinical signs or blood work)

(Miro' et al., World Congress of Veterinary Dermatology 2008)

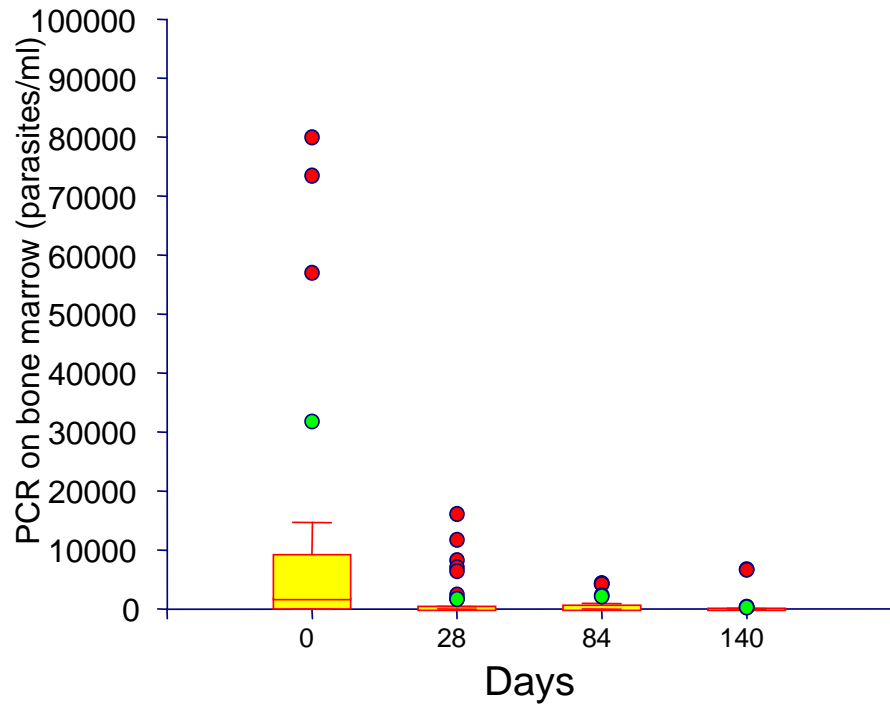
Clinical studies in dogs



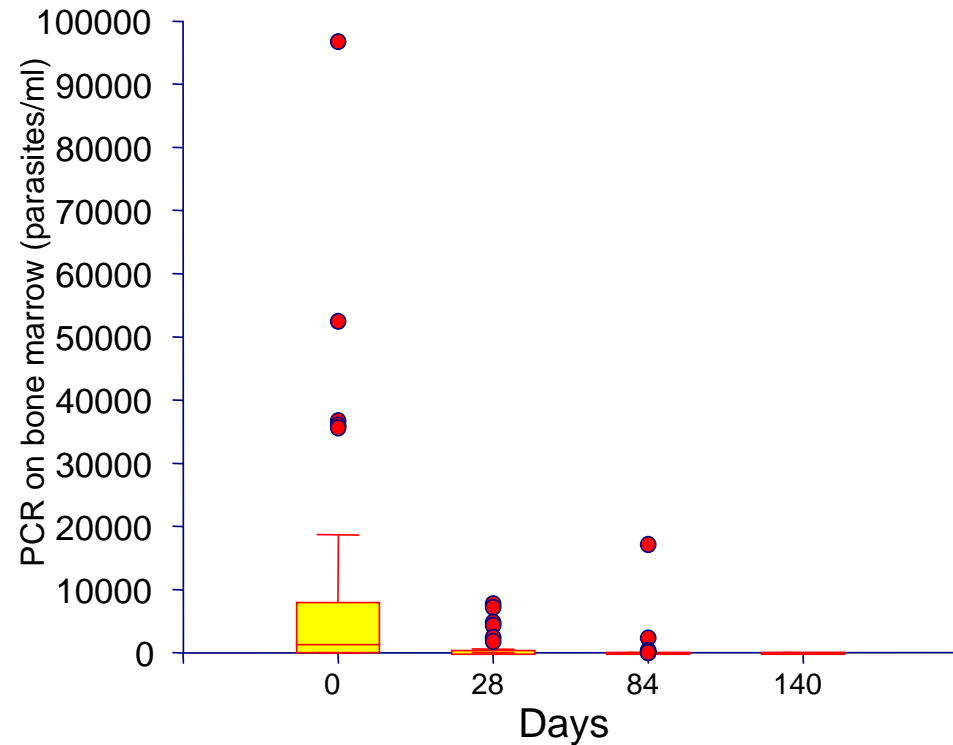
(Miro' et al., World Congress of Veterinary Dermatology 2008)

Clinical studies in dogs

Miltefosine+Allopurinol



Glucantime+Allopurinol



(Miro' et al., World Congress of Veterinary Dermatology 2008)

Rationale for using Alternative Protocols

- Dogs that do not respond (or have prompt relapse)
- Limited owner's compliance
- Intolerance / Side effects





