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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/](http://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)

# 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
<b>A</b>	<b>Exposure or Subpatent Infection</b>	<b>NOT TO TREAT</b>

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

Stage	Definition	Description
<b>C</b>	<b>Disease</b>	
<b>D</b>	<b>Severe Disease</b>	<b>TREAT</b>

# 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



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# **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%)

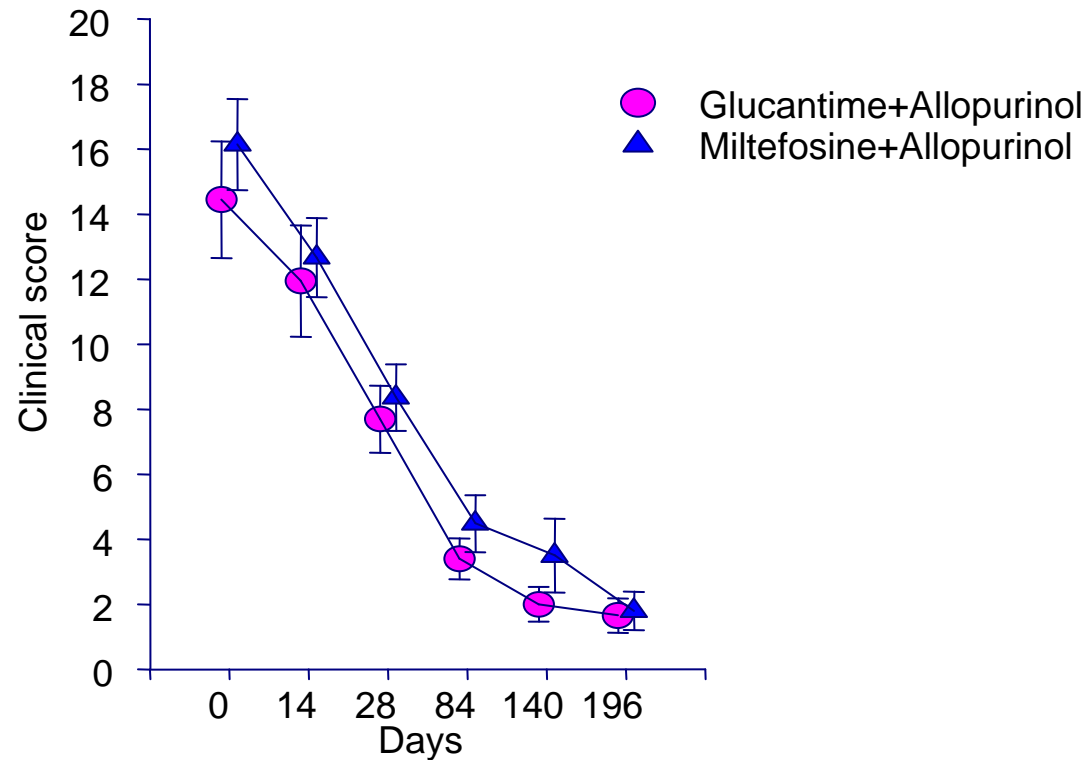
(Mateo et al., Parasitol Res 2009)

# 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)

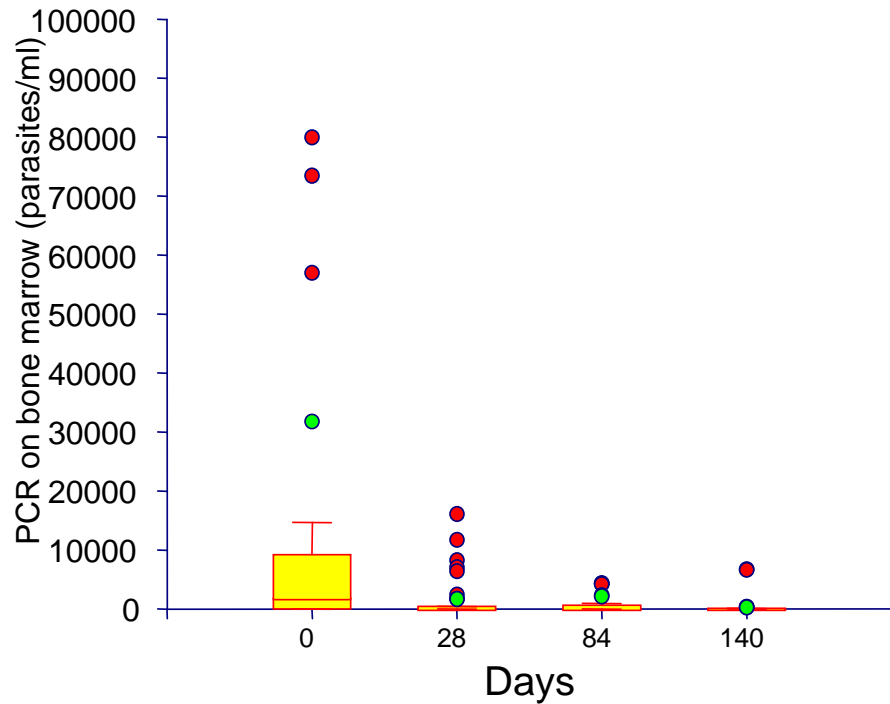
# Clinical studies in dogs



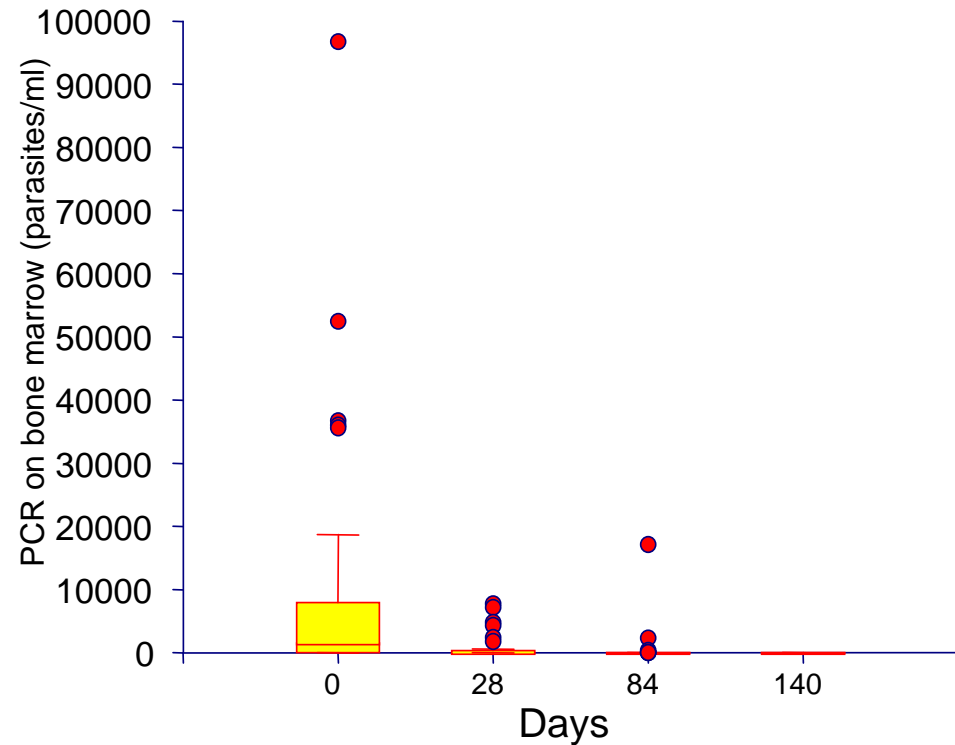
(Miro' et al., World Congress of Veterinary Dermatology 2008)

# Clinical studies in dogs

## Miltefosine+Allopurinol



## Glucantime+Allopurinol



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

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- Dogs that do not respond (or have prompt relapse)
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