Chronic Murine Chromoblastomycosis: Therapeutic Comparison

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CHROMOBLASTOMYCOSIS

- Cutaneous and subcutaneous chronic infection caused by the traumatic inoculation of certain dematiaceous fungi
- Cause of incapacitating deformities
- This disease is found world wide, but occurs with higher frequency in tropical countries

Diagnosis

§ Direct examination (warty nodules)

Clinical characteristics:

- Nodular lesions
- Verrucose hyperkeratotic forms
- Scaly plaques
- Scarring atrophic skin lesions

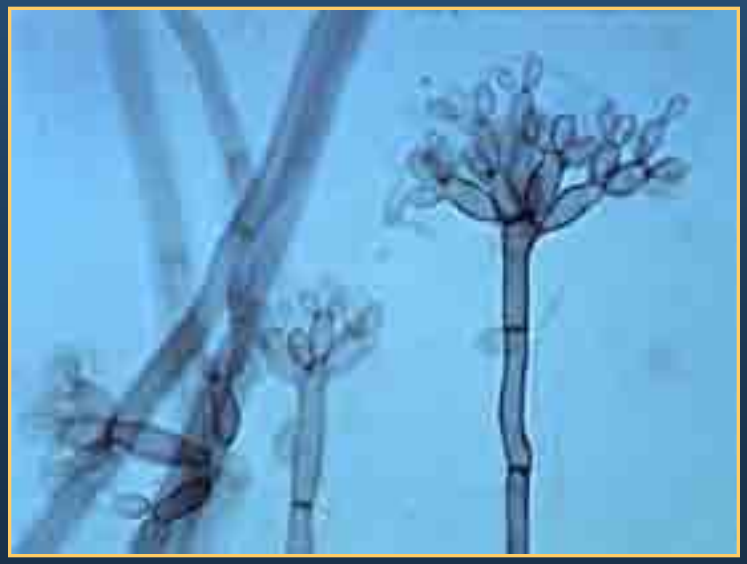
Diagnosis

- Culture
- Histology (presence of muriform cells or Medlar bodies)

Main fungi causing the disease

- *Fonsecaea pedrosoi*
- *Cladophialophora carrionii, Phialophora verrucosa, Rhinocladiella aquaspersa, Cladophialophora bopii*

- *Exophiala jeanselmei, Exophiala spinifera, Exophiala dermatitidis*



Treatment

- Physical methods
  - » Surgery
  - » Thermotherapy
  - » Laser surgery
- Chemotherapy
  - » Itraconazole
  - » Terbinafine
  - » Posaconazole
  - » Voriconazole

Objectives

- To establish a chronic murine model of Chromoblastomycosis

- To compare the evolution of the infection after the administration of new generation treatments (posaconazole and voriconazole) against the most used therapies (itraconazole and terbinafine)

Model establishment

Mice	Inf. route	Response
• IMMUNOCOMP.	IV	ACUTE INFECTION
• IMMUNOSUP. (CORTISONE)	IV	ACUTE INFECTION
• IMMUNOCOMP.	SC	ACUTE INFECTION
• IMMUNOSUP. (ATHYMICS)	SC	CHRONIC INFECTION
• IMMUNOCOMP. (MICE PUPS)	IP	ACUTE INFECTION
• IMMUNOCOMP.	IP	CHRONIC INFECTION

Materials & methods

- Strains: *F. pedrosoi*: FMR 5211, FMR 6630
  P. verrucosa FMR 5210
- Mice: CD1/nude (athymics)

- Ceftazidime: 0.05 mL (150mg/kg) s.c.
- Anaesthetic: isoflurane

Subcutaneous infection in nude mice

$3x10^7$ cfu/mL in 0.1 mL

12 months post-infection strain FMR 6630

Materials & methods

- Treatments: (3 weeks after the infection)
  - Posaconazole 10, 20 mg/kg/day (orally)
  - Voriconazole 10, 20 mg/kg/day (orally) + 0.25 ml of grapefruit juice
  - Itraconazole 25, 50 mg/kg/day (orally)
  - Terbinafine 150, 250 mg/kg/day (orally)

All treatments were administered for 4 months

In vitro activitiy of antifungal drugs against the isolate *F.pedrosoi* FMR 6630

MICs (mg/ml)				
	PSC	**VRC**	**ITZ**	**TRB**
6630	0.12	0.12	0.5	0.12

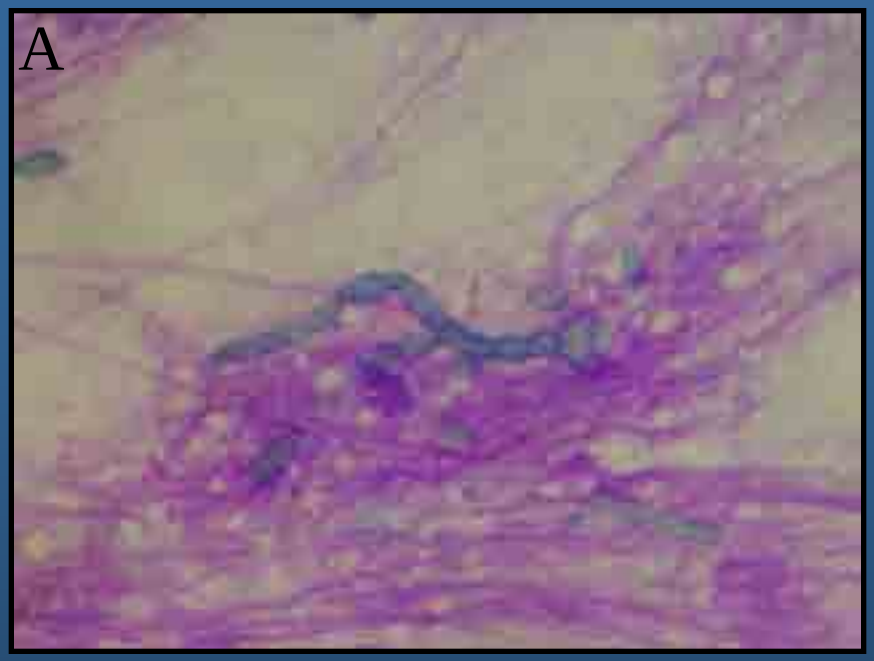
Materials & methods

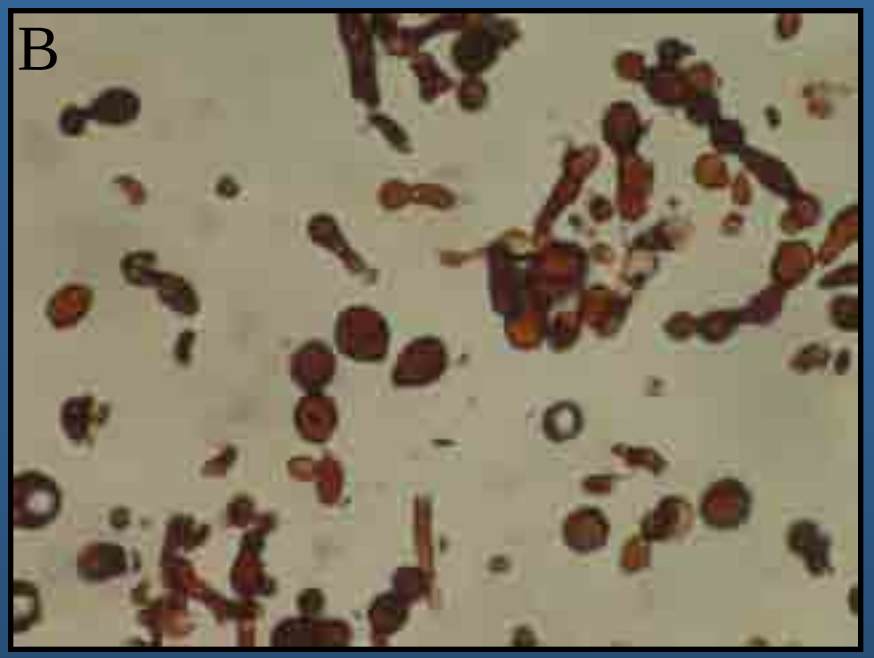
- Lesions were measured at 3 weeks intervals

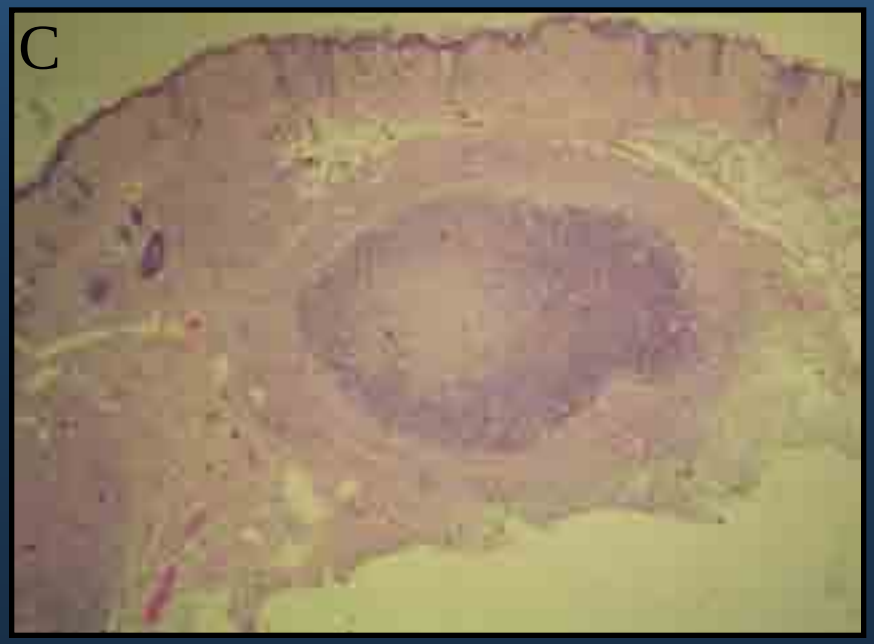
Culture

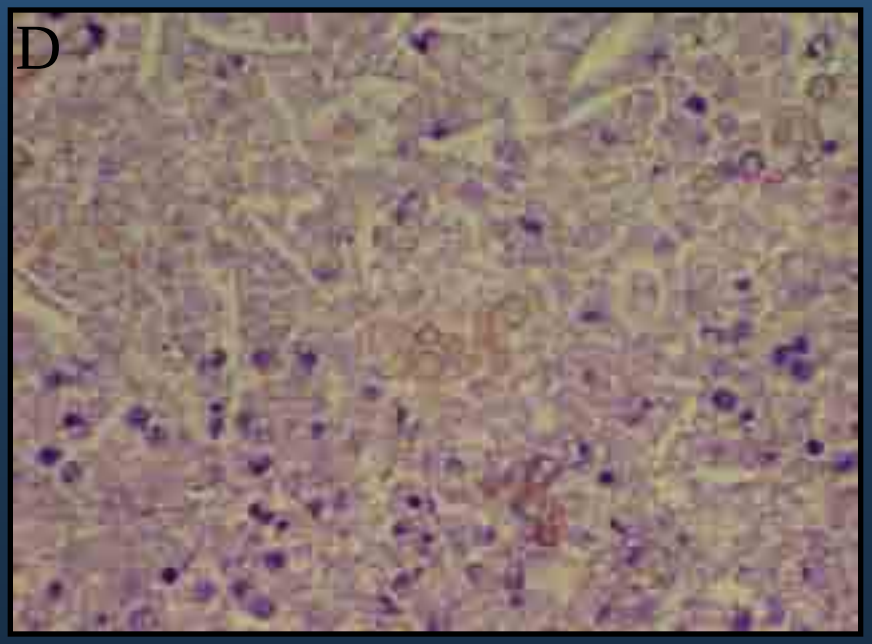
Skin lesions were cultured at the end of the therapy

Histology



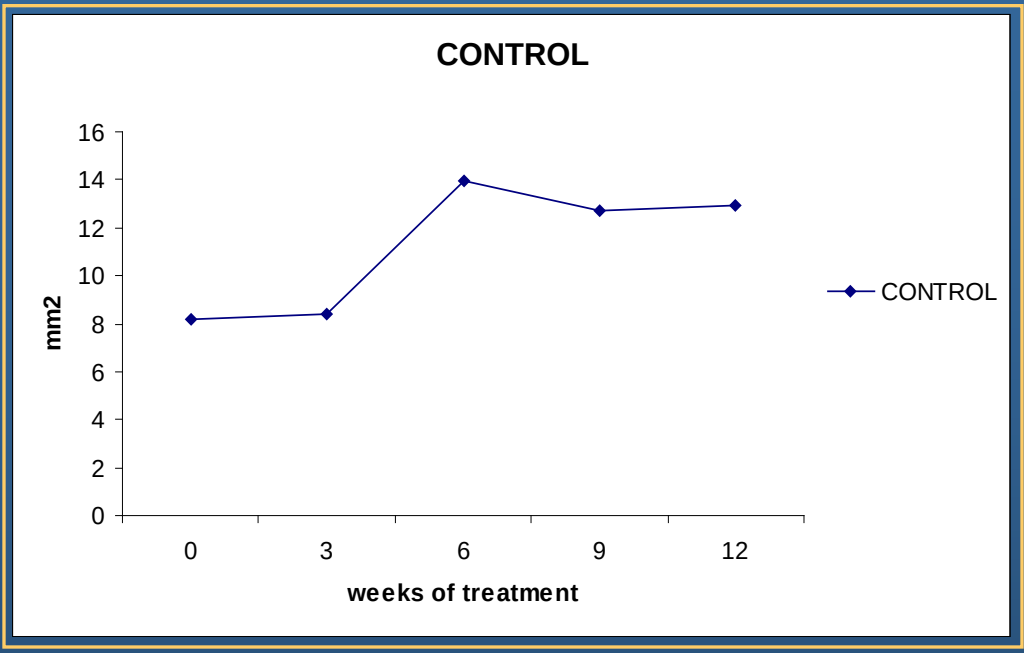


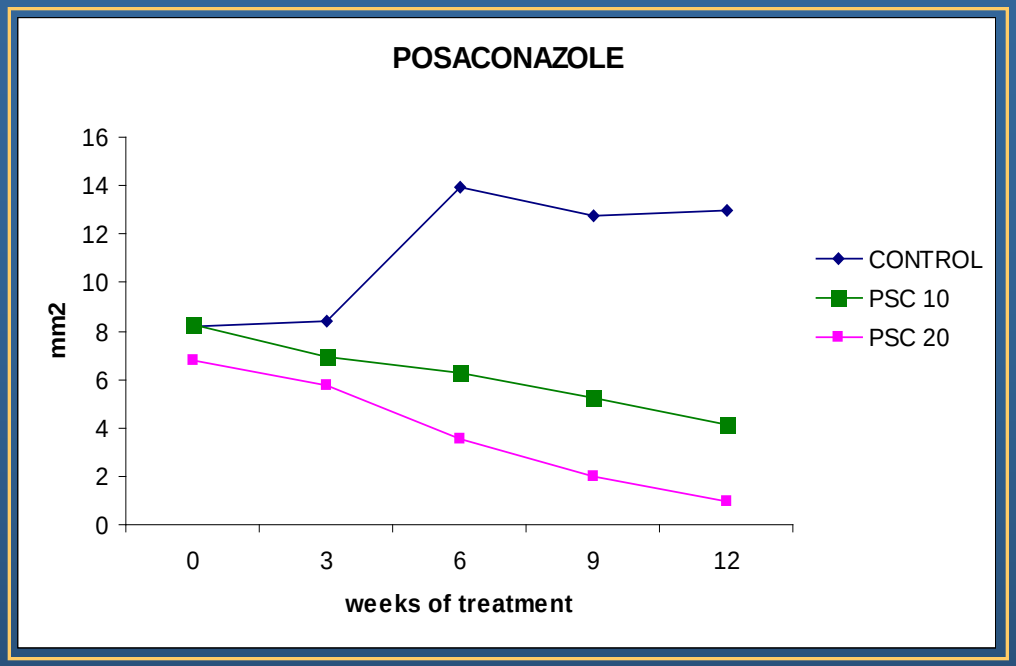


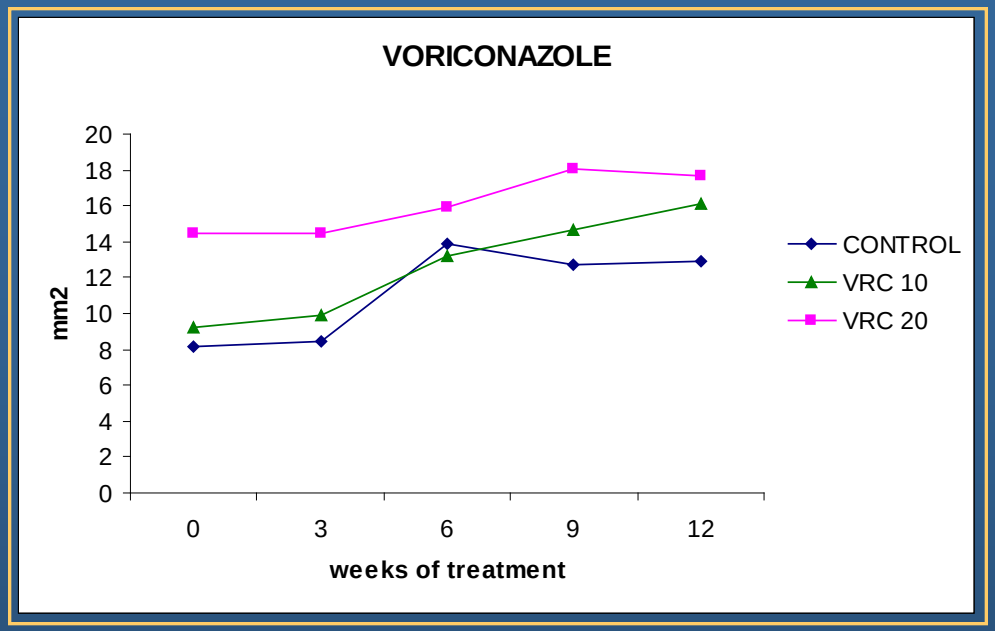


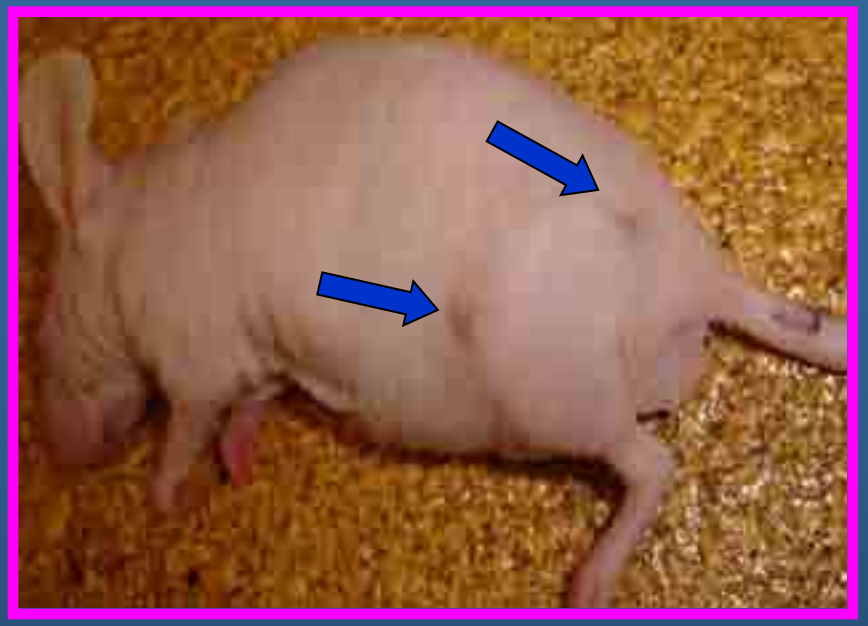
Results

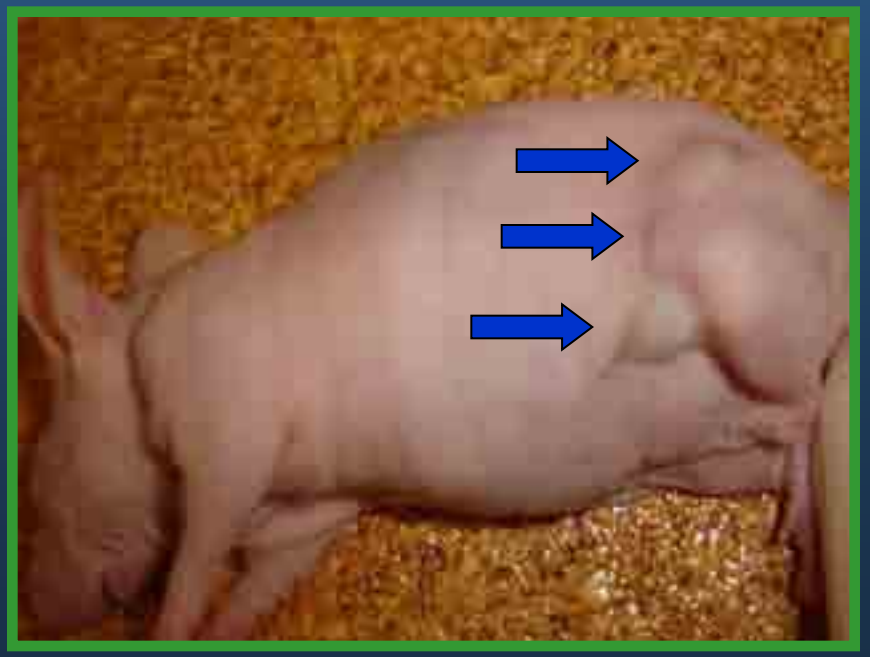
Control group

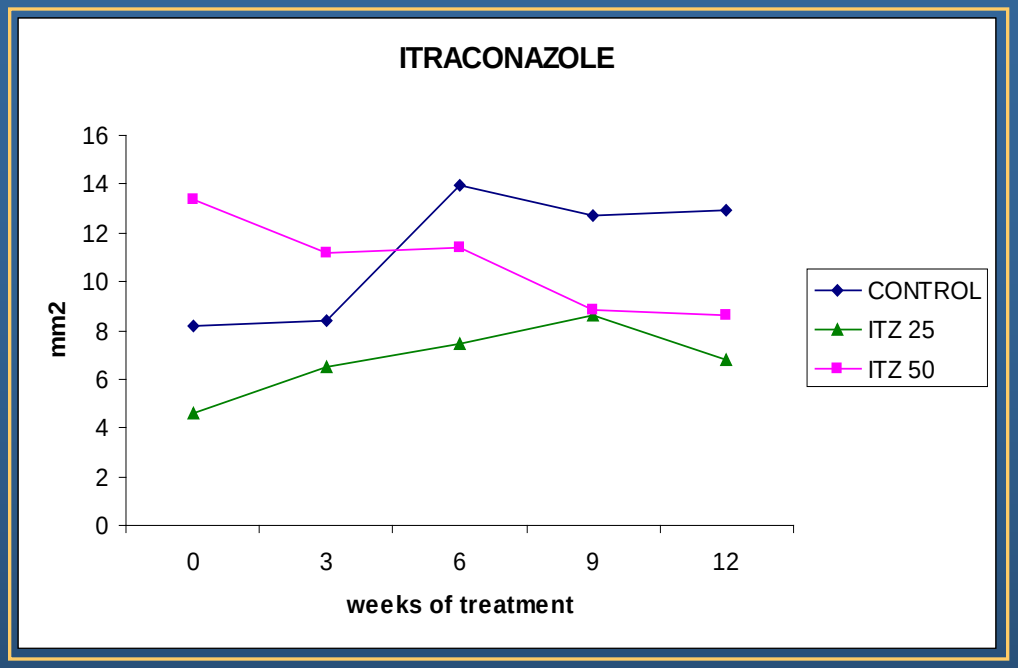


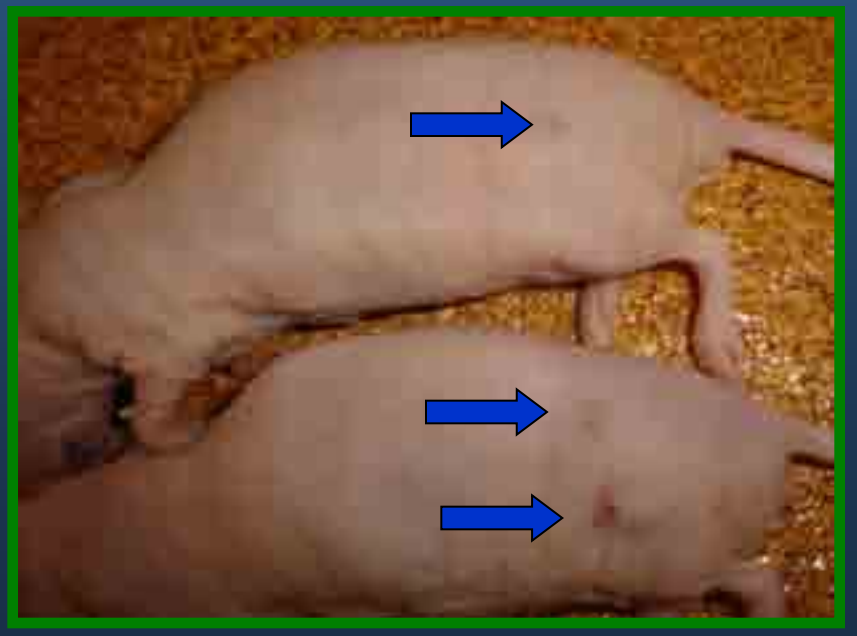

POSACONAZOLE
16
14
12
10
8
6
4
2
0
mm2
0
3
6
9
12
weeks of treatment
CONTROL
PSC 10
PSC 20

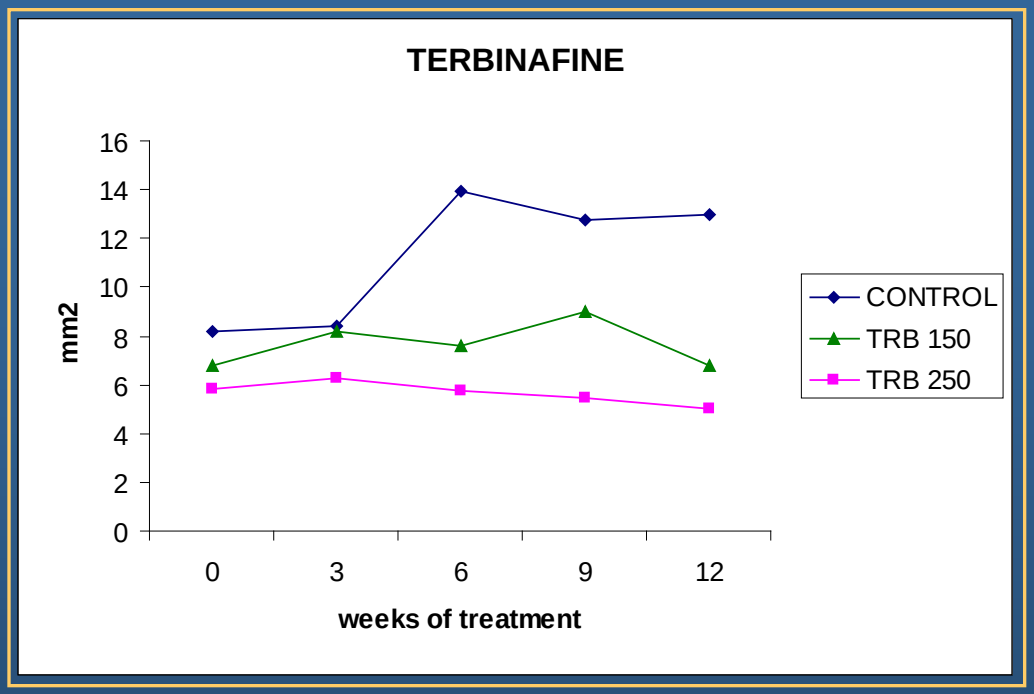

VORICONAZOLE
20
18
16
14
12
10
8
6
4
2
0
mm2
0
3
6
9
12
weeks of treatment
CONTROL
VRC 10
VRC 20

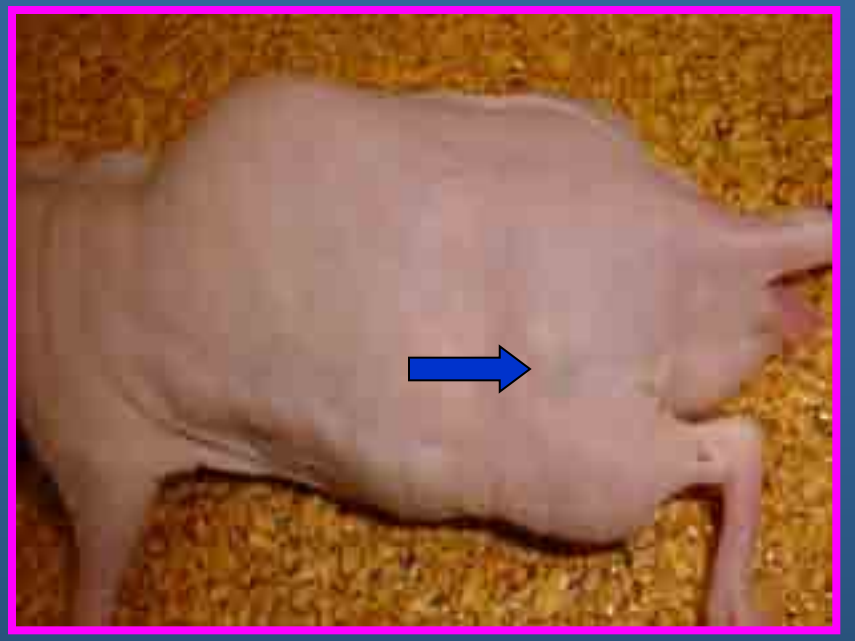





ITRACONAZOLE
16
14
12
10
8
6
4
2
0
mm2
0
3
6
9
12
weeks of treatment
CONTROL
ITZ 25
ITZ 50




TERBINAFINE
16
14
12
10
8
6
4
2
0
mm2
0
3
6
9
12
weeks of treatment
CONTROL
TRB 150
TRB 250



Results

Group 1	Group 2	Mann Whitney p-value
Control	ITZ 25	0.222
Control	ITZ 50	0.009
Control	PSC 10	*0.076*
Control	PSC 20	0.009
Control	TRB 150	0.117
Control	TRB 250	0.047
Control	VRC 10	0.917
Control	VRC 20	0.222

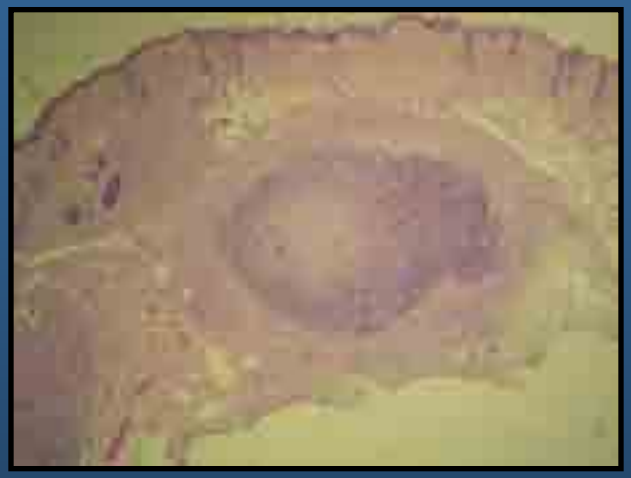
P-value < 0.05

Results

Groups	Changes in the lesion sizes after 12 weeks (%)	Positive cultures (%)
CONTROL	+82.6	100
ITZ 25	+23.9	100
ITZ 50	-24.3	75
PSC 10	-20.8	75
PSC 20	-69.6	50
TRB 150	+13.7	100
TRB 250	-0.6	100
VRC 10	+84.2	100
VRC 20	+10.5	100

Histological study

CONTROL



CONTROL

VORICONAZOLE

TERBINAFINE

ITRACONAZOLE

POSACONAZOLE

Conclusions

- The results demonstrated PSC as an alternative in the treatment of Chromoblastomycosis.
- VRC showed modest results in this model of Chromoblastomycosis.

THANK YOU!