# 2006 ACR REVIEW

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2007.1.13 SSc研究班会議

# 2006年の演題

- Concurrent Session
  An update on stem cell transplantation:　6演題
  Pathogenesis, animal models and genetics:　6演題
  Clinical Trials:　6演題
- Plenary Session　1演題
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# Concurrent Session

## An update on stem cell transplantation

1. High dose immunosuppressive therapy (HDIT) with peripheral blood stem cell transplantation (PBSCT) １０名　Northwestern Univ
2. HDIT without transplantation ６名　Johns Hopkins
3. HDIT with PBSCT １０名　Kyushu Univ
4. 5-year follow-up of HDIT with PBSCT ３４名　Fred Hutchinson Cancer Research Center, Seattle
5. HDIT with PBSCT ２６名　Radboud Univ, Netherlands
6. Simvastatin treatment to endothelial damage Milano, Italy

# Regimen of HDIT

1. Cy: 200 mg/kg, ATG: 7.5 mg/kg
2. Cy: 50 mg/kg  4 days
3. Cy: 2 g/$m^2$ 2 days
4. Cy: 60 mg/kg 2 days, ATG: 15 mg/kg 6 days, total body irradiation: 400 Gy 2 days
5. Cy: total 4 g/$m^2$

# 結果

- TSSの改善はすべての研究で確認
- 心機能(EF)の改善は認めない。
- PBSCTを行わなかった研究では、６例中１例で、緑膿菌感染により死亡。
- ５年経過観察研究では、３４例中、１２例で死亡。

# Results of 5-year follow up study

| | baseline | 4(1-8)年後 |
|---|---|---|
| Cre | 0.78 | +0.25, p=0.003 |
| EF | 63.24 | -2.37, p=0.06 |
| FVC | 71.53 | +2.11, p=0.50 |
| mHAQ | 1.85 | -1.03, p<0.0001 |
| mTSS | 30.1 | -22.08, p<0.0001 |
| DLco | 60.9 | -7.07, p=0.02 |

３４例のdcSSc（発症４年以内）の登録で、
５年後の生存率は６４％

# Concurrent Session

## Clinical Trials

1. Outcome at 24-months treated by cyclophosphamide therapy
2. Trial of Tadalafil (PDE5I) in Raynaud
3. Trial of a topical gel formulation of NTG (MQX-503) in Raynaud
4. Rituximab
5. Infliximab
6. Rapamycin

# Design
## Inclusion Criteria

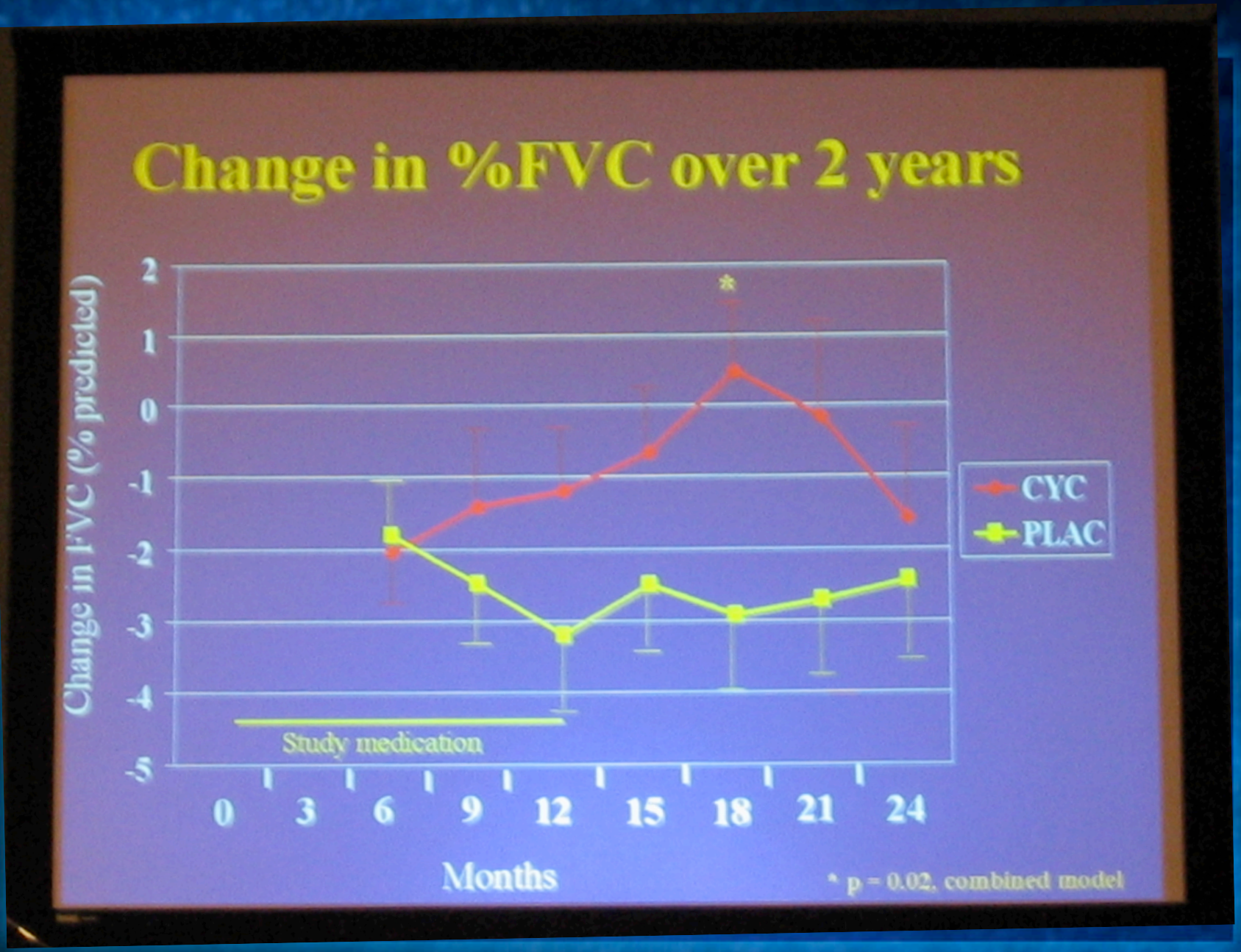
- First phase of screening for entry
  - Systemic sclerosis (by ACR criteria)
  - ≤ 7 years of SSc from onset of the first non-Raynaud symptom typical of SSc
  - FVC 45-85% of predicted
  - Level 2 dyspnea on Mahler Magnitude of Task index (3 flights of stairs)
  - Aged ≥18 y/o
  - Male or female
  - Diffuse or limited cutaneous scleroderma

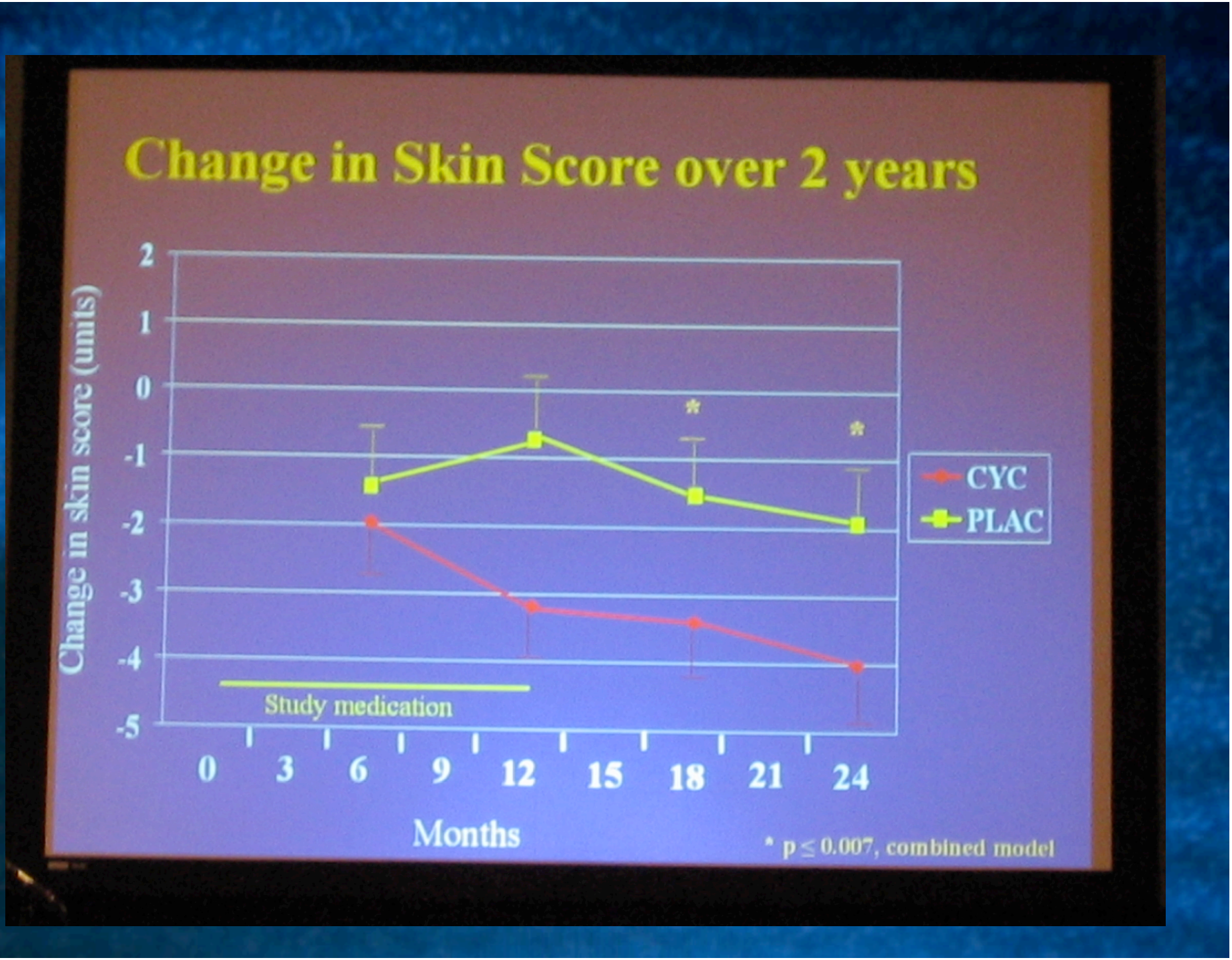
# Study Design

Cy 1 mg/kg/dayの内服から始めて、2 mg/kg/dayまで、増量。12ヶ月継続。

または

同じカプセルの同じ量をプラセボとして内服


Change in %FVC over 2 years
Change in FVC (% predicted)
2
1
0
-1
-2
-3
-4
-5
*
CYC
PLAC
Study medication
0
3
6
9
12
15
18
21
24
Months
* p = 0.02, combined model


Change in Skin Score over 2 years
Change in skin score (units)
2
1
0
-1
-2
-3
-4
-5
*
*
CYC
PLAC
Study medication
0
3
6
9
12
15
18
21
24
Months
* p ≤ 0.007, combined model

# Conclusions

- These data suggest that either:
  - CYC needs to be continued for a longer period of time (despite the toxicity)

**OR**

  - an alternative, less toxic medication should be explored for longer term use in SSc lung disease.

# Concurrent Session

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# Summary

- There was no difference between tadalafil and placebo on measures of RP
- Tadalafil was well tolerated
- Present data do not support the use of tadalafil as a therapy for RP secondary to SSc
- Our study has a 60% power for a 20% treatment effect
- Placebo effect remains a prominent issue in RP clinical trial design

# Concurrent Session

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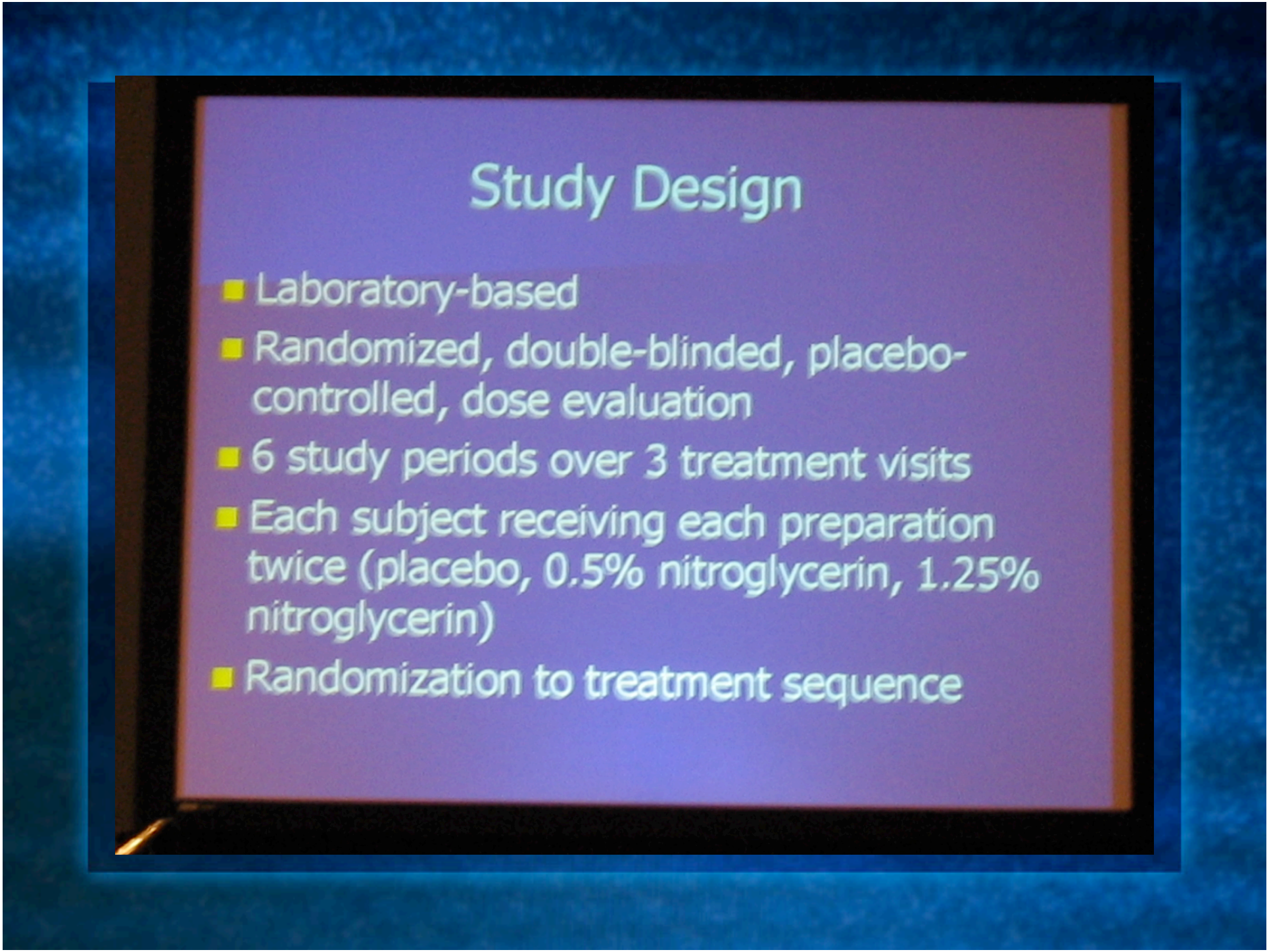
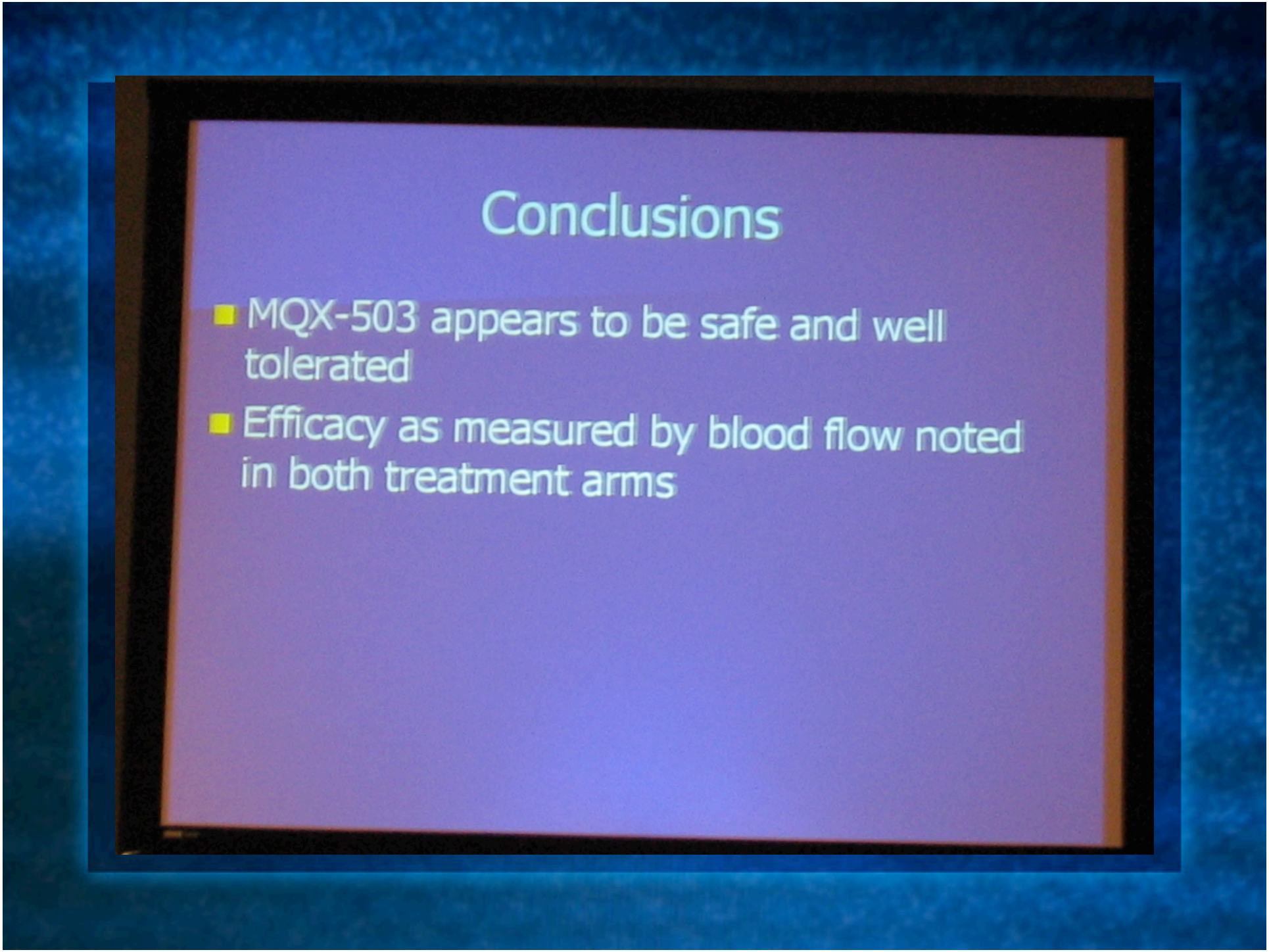

Study Design
Laboratory-based
Randomized, double-blinded, placebo-controlled, dose evaluation
6 study periods over 3 treatment visits
Each subject receiving each preparation twice (placebo, 0.5% nitroglycerin, 1.25% nitroglycerin)
Randomization to treatment sequence


Conclusions
MQX-503 appears to be safe and well tolerated
Efficacy as measured by blood flow noted in both treatment arms

# Concurrent Session

## Clinical Trials

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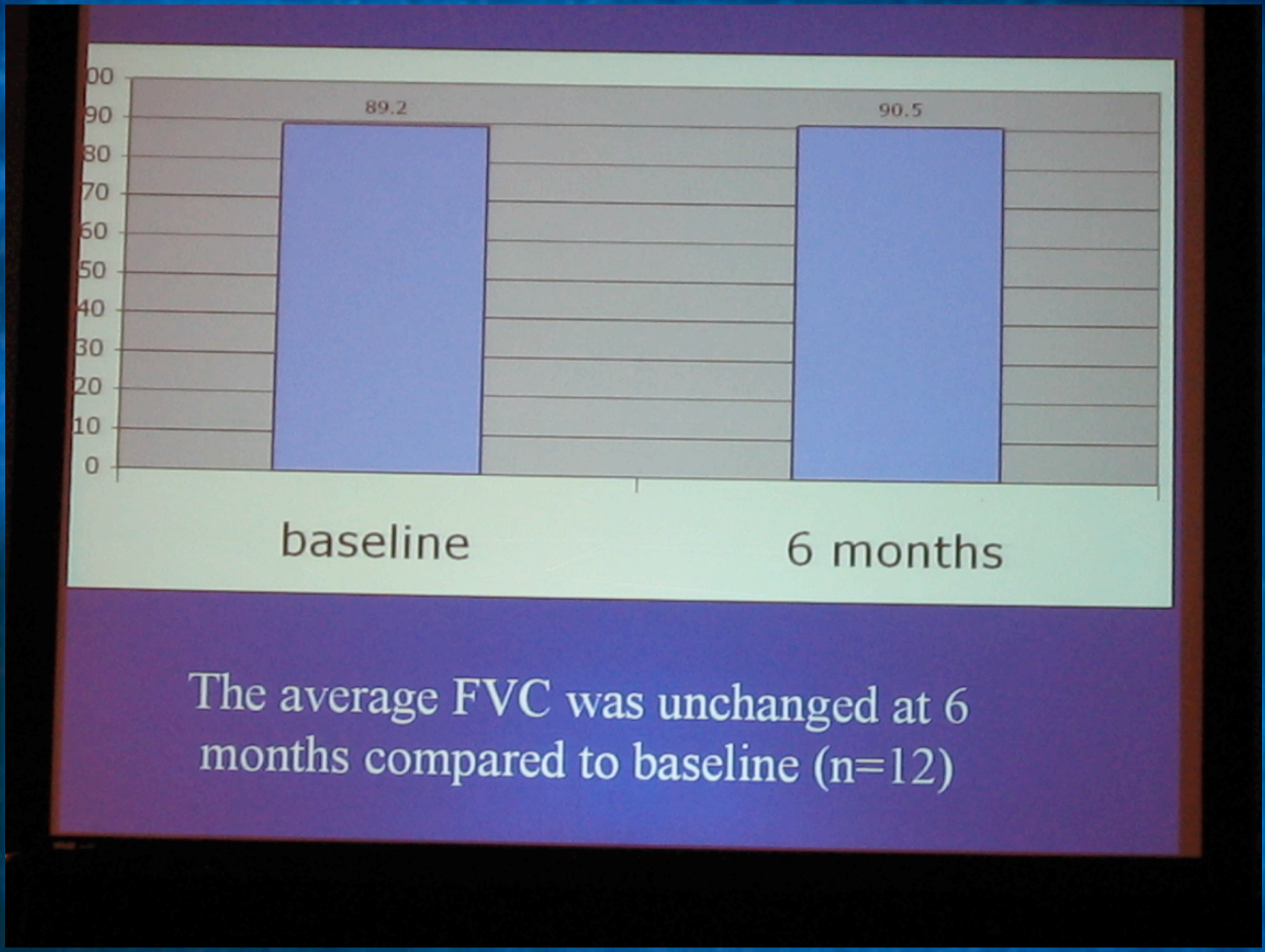
# Open label trial of Rituximab (1 gm x 2 doses) in 15 patients with early diffuse systemic sclerosis

- Patients must have first non-Raynaud's disease manifestation within 18 months of trial entry
  - Attempt to treat "immunologically active" patients
- No severe pulmonary disease (FVC and DLCO greater than 50% predicted)
- No significant cardiac disease
- No immunosuppressive (MTX allowed later-1 patient)


00
90
80
70
60
50
40
30
20
10
0
89.2
90.5
baseline
6 months
The average FVC was unchanged at 6 months compared to baseline (n=12)

# SUMMARY

- Rituximab appears safe in patients with diffuse cutaneous systemic sclerosis
- Rituximab did not show a benefit on clinical skin disease, but the small patient number, highly variable progression and lack of a control population limit the interpretation of this observation
- Rituximab treated patients showed no evidence of progressive end-organ damage, commonly seen in this patient population
- Rituximab treatment was associated with decreased myofibroblasts-a biomarker of skin disease

# An Open-label Pilot Study of Infliximab Therapy in Diffuse Cutaneous Systemic Sclerosis

CP Denton[1], CM Black[1], M Engelhart[2], N Tvede[2], K Khan[1], PE Carreira[3], F Diaz Gonzalez[4], FH van den Hoogen[5].

[1]Royal Free Hospital, London, United Kingdom; [2]Herlev University Hospital and Rigshospitalet, Copenhagen, Denmark; [3]Hospital 12 de Octubre, Madrid, Spain; [4]University Hospital, Tenerife, Canary Islands; [5]University Hospital, Nijmegen, The Netherlands

# Study Protocol

- １６例の強皮症患者に対して、0, 2, 6, 14, 22週後にそれぞれinfliximab 5 mg/kgを点滴静注
- ２６週後の臨床症状を評価

# Outcome markers: clinical

| utcome* | baseline | 6 weeks | 22 weeks | 26 weeks |
|---|---|---|---|---|
| RSS | 26 (11,45) | 29 (11,44) | 17 (6,46) | 22 (6,48) |
| AQ-DI | 1.63 (0,3) | 1.5 (0,2.88) | | 1.5 (0, 2.63) |
| S | 16 (0,28) | 13 (0,26) | | 13 (0,29) |
| AS[1] | 65 (34,78) | 56 (22,87) | | 61 (29,89) |

results reported are median (range)

* p = NS for all as compared to baseline

[1] VAS is the physician global assessment

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# Study Design

- 18名のdiffuse cutaneous SSc　発症５年以内
- Randomized, control (MTX) trial
- MTX: 15 mg/week
- Rapamycin: 1-11 mg/day 血中濃度が10-15 mg/mlになるように調整
- 評価は、４８週にて行う。

# Change scores within Rx group

## (p-values < 0.1 in green)

| | RAPA | | MTX | |
|---|---|---|---|---|
| Variable | Chng score | p-value* | Chng score | p-value* |
| Fist closure | -3.8 ± 3.3 | 0.06 | 0.3 ± 4.6 | 0.87 |
| FVC (% pred) | 10.5 ± 6.6 | 0.05 | 1.2 ± 14.1 | 0.86 |
| Hgb | -2.0 ± 1.3 | 0.03 | 0.5 ± 1.3 | 0.45 |
| MD global | 8.4 ± 7.5 | 0.07 | 5.5 ± 11.2 | 0.28 |
| Pt global | 11.5 ± 6.2 | 0.03 | 11.0 ± 31.7 | 0.48 |
| Skin score | -5.6 ± 3.9 | 0.03 | 6.9 ± 6.1 | 0.04 |

Wilcoxon rank-sum

# Adverse effects

Hypertriglyceridemia

2名 2205 mg/dl, 3265 mg/dl

rapamycinの中止により、改善

# Plenary Session III

Novel role of c-Abl tyrosine kinase in profibrotic TGF-beta response: selective modulation by the anticancer drug Imatinib methulate (Gleevec)

Ishida W, Takehara K, Varga J, et al

# Concurrent Session

## Pathogenesis, Animal models and Genetics

- TGF-βのシグナル伝達に関わるnon-Smad因子の検討:
  Egr-1 (Varga J et al)とc-Abl (Distler O et al)

- CD40-CD40L　Kuwana M

- Allograft inflammatory factor 1 (AIF-1)
  Jimenez SA et al

# Poster Session (86 titles)

- Long-term effects of Bosentan in PAH related to CTD: TRUST study

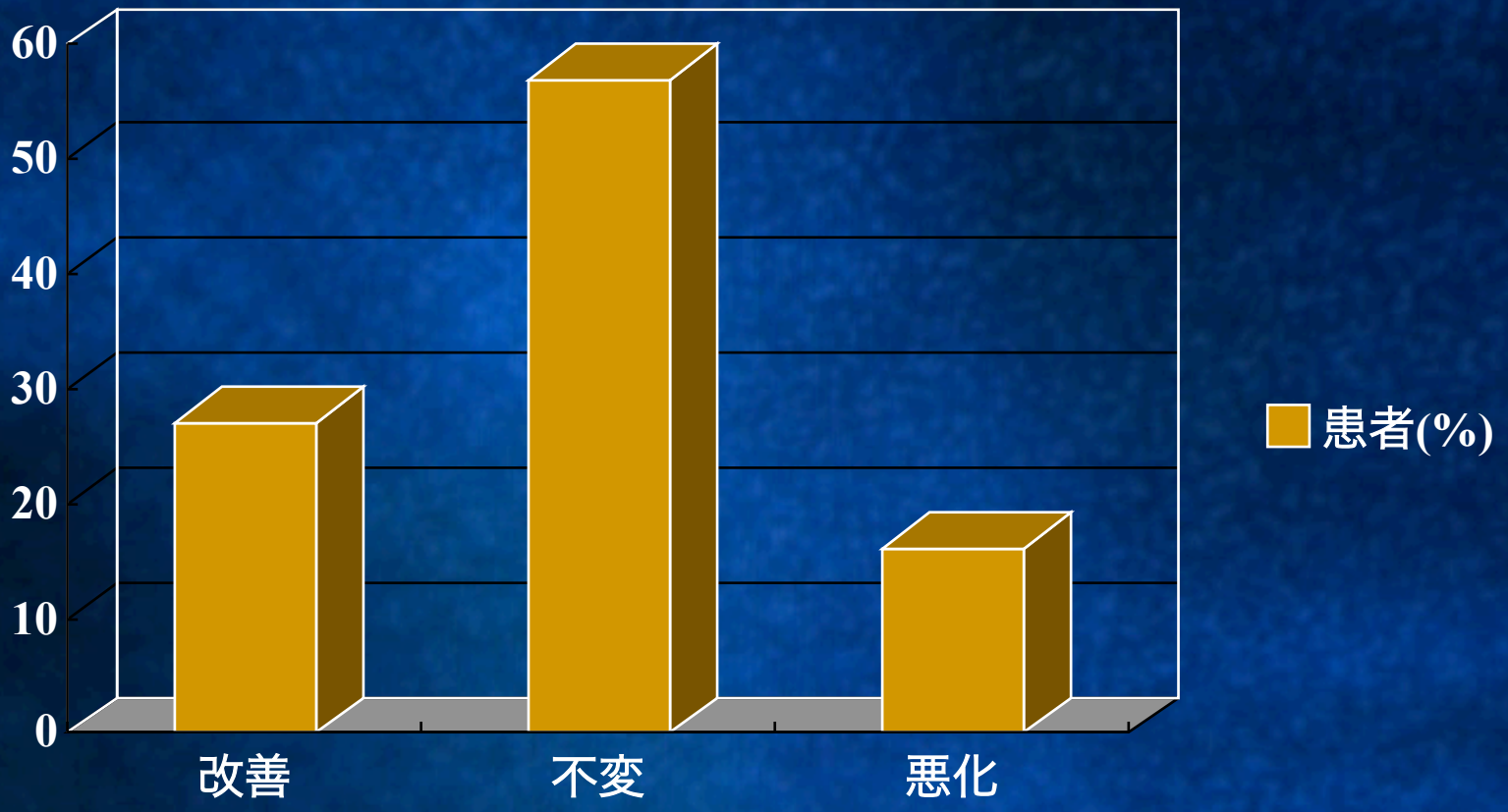
PAH(WHO III） 53例の48週の観察

ISSc: 29, dSSc 13, Overlap 6, SLE 5

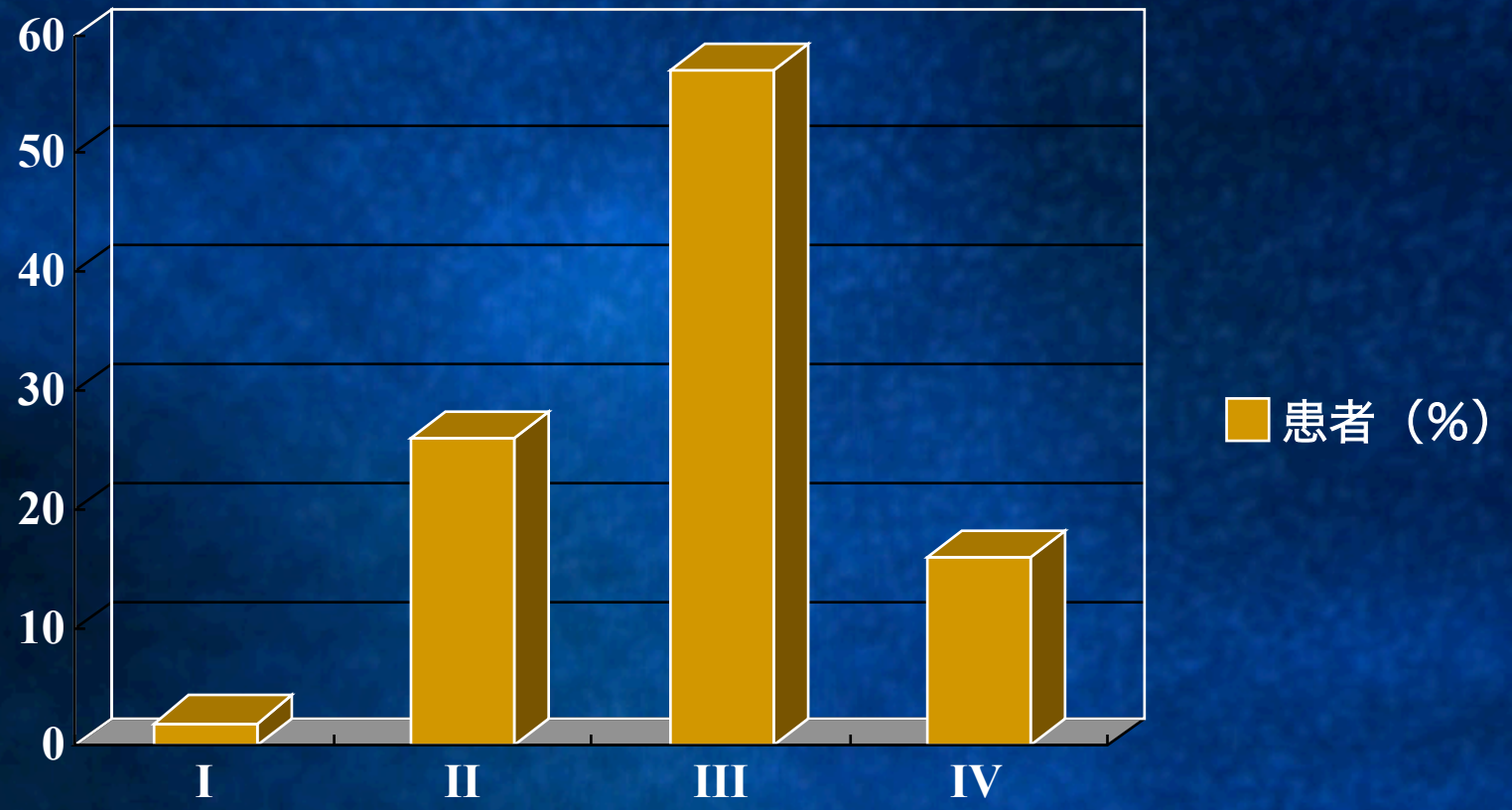
48週の観察が行えた症例は36例

4名の死亡(8%)

# WHO分類での改善度：48週



# 48週でのWHO分類



# Functional correlates of reduction of digital ulcers by bosentan therapy in patients with SSc

手指の皮膚潰瘍に対するボセンタンの効果

1. RAPIDS-1 (RCT study)
2. OLE (open label extension to RAPIDS-1)
3. RAPIDS-2 (RCT study)

3種類の研究で新たな皮膚潰瘍の抑制効果が示され、その結果、SHAQによるQOL評価が改善した。

# Mycophenolate Mofetil (MMF, セルセプト)の有効性

- 発症３年以内のalveolitisを有する7例と、mTSS>15以上の９例を対象とした
- mPSL pulse (15 mg/kg)　３日間を月に１回、６ヶ月間

  MMF　　１ｇ 分2 最初の1週間

  　　２ｇ 分2　その後1年間

  経口PSL　5-10 mg/day　1年間

# 12ヶ月の治療効果

| | Baseline | 6mo | 12mo | P |
|---|---|---|---|---|
| TSS | 20 | 14 | 13 | <0.0001 |
| HAQ | 1.1 | 0.7 | 0.6 | 0.021 |
| VC (%) | 85 | 90 | 93 | 0.06 |
| DLco (%) | 71 | 80 | 80 | <0.0001 |
| 6MWT | 505 | 564 | 562 | 0.005 |

# 治療方法のまとめ

- 皮膚硬化
  HDIT、シクロホスファミド、MMF
- 間質性肺病変
  シクロホスファミド、MMF
- 肺動脈性肺高血圧症
  ボセンタン
- 動物実験レベルでの改善：Imatinib (Gleevec)