“Effect and safety of Mycophenolate Mofetil in Idiopathic Pulmonary Fibrosis. A retrospective study”.

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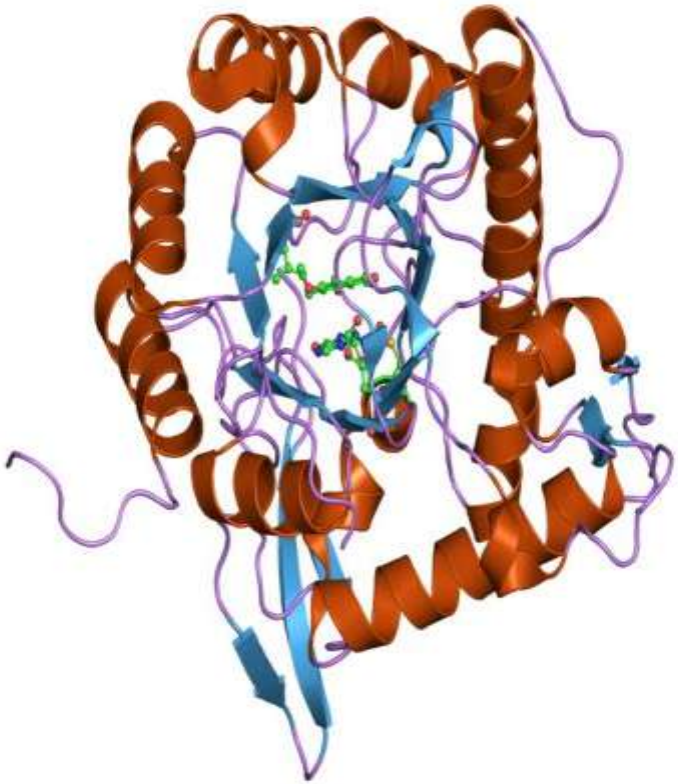
Mycophenolate Mofetil (MMF) (I)

- **IMDPH inhibition (MMF metabolite-mycophenolic acid)** **(Jayne D. Curr Opin Nephrol Hypertens 1999.)**
- **Purine biosynthesis**
- **Inhibition T-cell proliferation**
- **Downstream effect on adhesion to endothelial cells**
- **Immunosupression**
- **Immunomodulation**

IMP dehydrogenase is an enzyme that converts inosine monophosphate to xanthosine monophosphate.[2][3][4][5]

inosine 5'-phosphate + NAD^+ + H_2O —> xanthosine 5'-phosphate + NADH + H^+



Mycophenolate Mofetil (MMF) (II)

- **Rejection prevention after solid-organ transplantation**
  Ciancio et al. Transplantation 2005, Kobashigawa et al. Transplantation 2005

- **Beneficial in lupus nephritis.** *Appel et al. Transplantation 2005*

- **Anti-proliferative properties.** *Waller et al. Transplant Proc 2005*

- **Anti-fibrotic properties (attenuation of TGF-b expression).**
  Guo et al. Lupus 2005

MMF and SSc-ILD

Rheumatology 2006;45:1005–1008
Advance Access publication 20 February 2006

5 pts SSc-ILD

Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease

FVC - DLCO improvement

S. N. C. Liossis, A. Bounas and A. P. Andonopoulos

13 pts SSc-ILD

Effect of Mycophenolate Mofetil on Pulmonary Function in Scleroderma-Associated Interstitial Lung Disease*

FVC improvement

Anthony J. Gerbino, MD; Christopher H. Goss, MD, FCCP; and Jerry A. Molitor, MD

CHEST / 133 / 2 / FEBRUARY, 2008

Aim – Nature of the study

- Determine safety and efficacy profile of MMF in IPF patients (no available data in current literature)

- Retrospective study

Study methodology

1. Identification of IPF patients (based on ATS/ERS 2000 criteria)
2. Per-os administration of 1.44 gr/d of MMF >6 mo
3. September 2006 – October 2008
4. Mean time from diagnosis to drug initiation = 9±2 mo
5. Assessment of routine laboratory tests (WBCs, Hct, liver enzymes)
6. Assessment of PFTs (FVC, DLco, TLC) at baseline - 6 - 12 mo post-treatment
7. Assessment of 6MWD, PA-aO_2 at baseline – 12 mo post-treatment
8. Assessment of HRCT at baseline – 12 mo post-treatment based on simple staging system (Goh N, Wells AU et al. Am J Respir Crit Care Med 2008; 177(11):1248-1254.

Results

Table 1. Baseline characteristics of the study population

Characteristics	Baseline data
Subjects	10
Male	10
Age (yrs)	63 (44-73)
Smokers	10
Ex-smokers	10
Non-smokers	0
Prior treatment (steroids) received	3
Other treatment received	3
VATS	6
sPAP (by echocardiography) mmHg	37.2 $\pm$ 19.6

Safety profile

No cases of liver toxicity, leucopenia, infection

Efficacy profile

Table 2. FVC, TLC, DL_{CO}, 6MWD and $P_{A-a}O_2$ at baseline and 6 and 12 month post MMF treatment

	Baseline	6 mo	12 mo	p-value [1]	p-value [2]
FVC (%)pred	59.2 ± 17.1	58.2 ± 17.2	55 ± 14.9	0.228	0.081
TLC (%)pred	53.9 +10.2	53.6 +12.3	52 ±12.8	0.702	0.081
DL_{CO} (%)pred	39.4 + 9.3	38.5 + 9	35.2 + 8.8	0.47	0.053
6MWD	441 +124	NA	421 + 123	NA	0.09
$P_{A-a}O_2$	27.4 +11.5	NA	27.7+11.2	NA	0.67

Table 3. HRCT scores before and after MMF treatment

Disease deterioration based on total disease extent and ground glass (GGO) extent

Patient	Disease Extent 0 mo	Reticular Extent 0 mo	GGO Extent 0 mo	Coarseness Reticulation 0 mo	Proportion GGO 0 mo	Disease Extent 12 mo	Reticular Extent 12 mo	GGO Extent 12 mo	Coarseness Reticulation 12 mo	Proportion GGO 12 mo
1	23	23	5,2	9	22,6	28	18,7	9,3	9	33,21
2	23	10,5	12,5	8	54	52	34,8	17,2	10	32
3	25	22,5	2,5	11	10	28	17,2	10,8	11	38,57
4	59	31,3	27,7	12	47	67	35,1	31,9	12	47,6
5	38	18,2	19,8	10	52,1	64	40,4	23,6	13	36,8
6	32	19,3	15,3	9	36,9	33	29,9	19,2	11	36,9
7	33	20,1	14,9	11	37,8	35	31,2	25,2	13	35,8
8	31	22,1	11,2	10	36,9	46	30,9	26,2	10	39,2
mean	33	20,7	13,6	10	37,02	44	29,7	20,42	11	37,5
p-value						0.002*	>0.05	0.02*	>0.05	>0.05

Figure 1

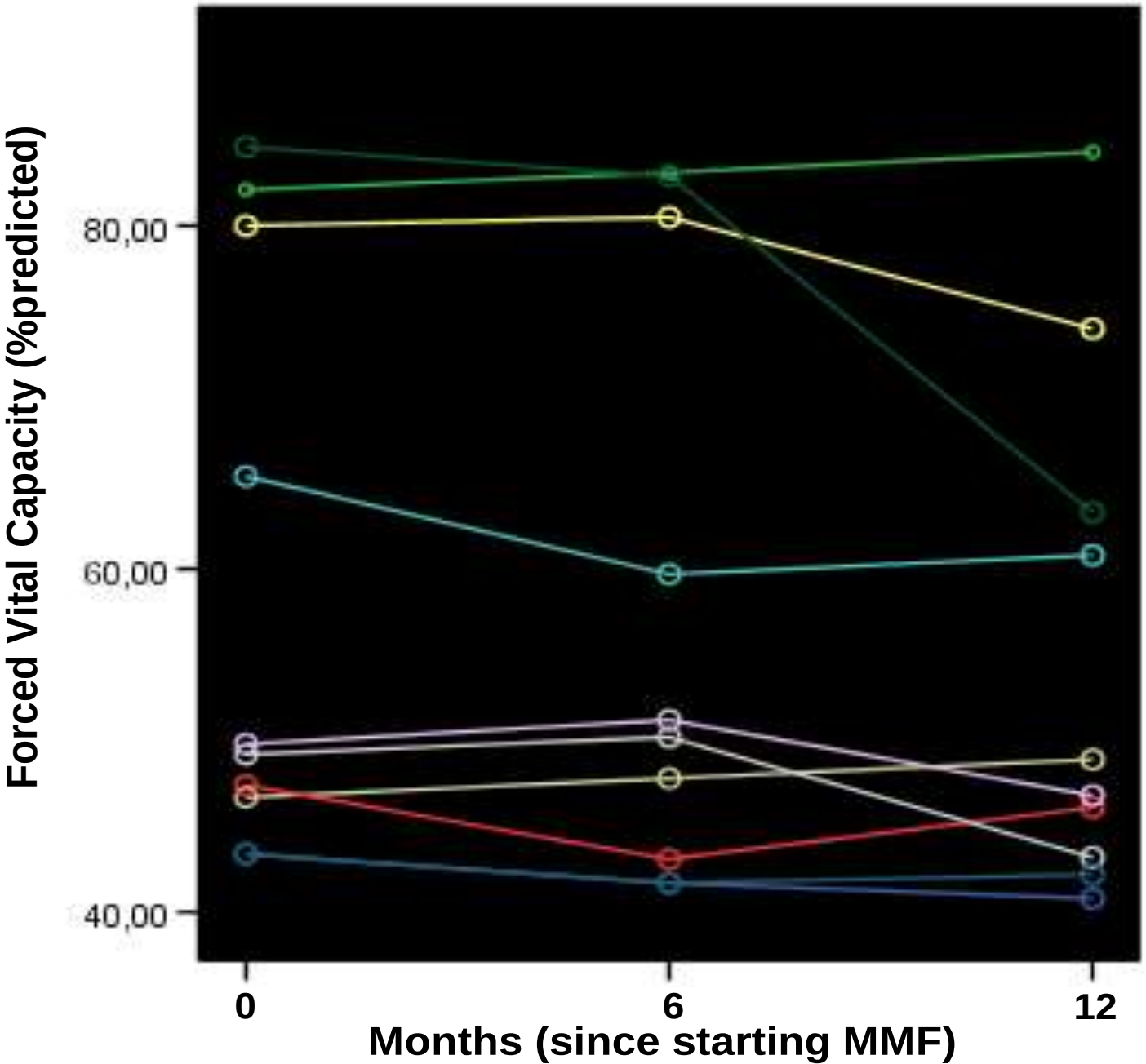

Forced Vital Capacity (%predicted)
80,00
60,00
40,00
0
6
12
Months (since starting MMF)

Figure 2

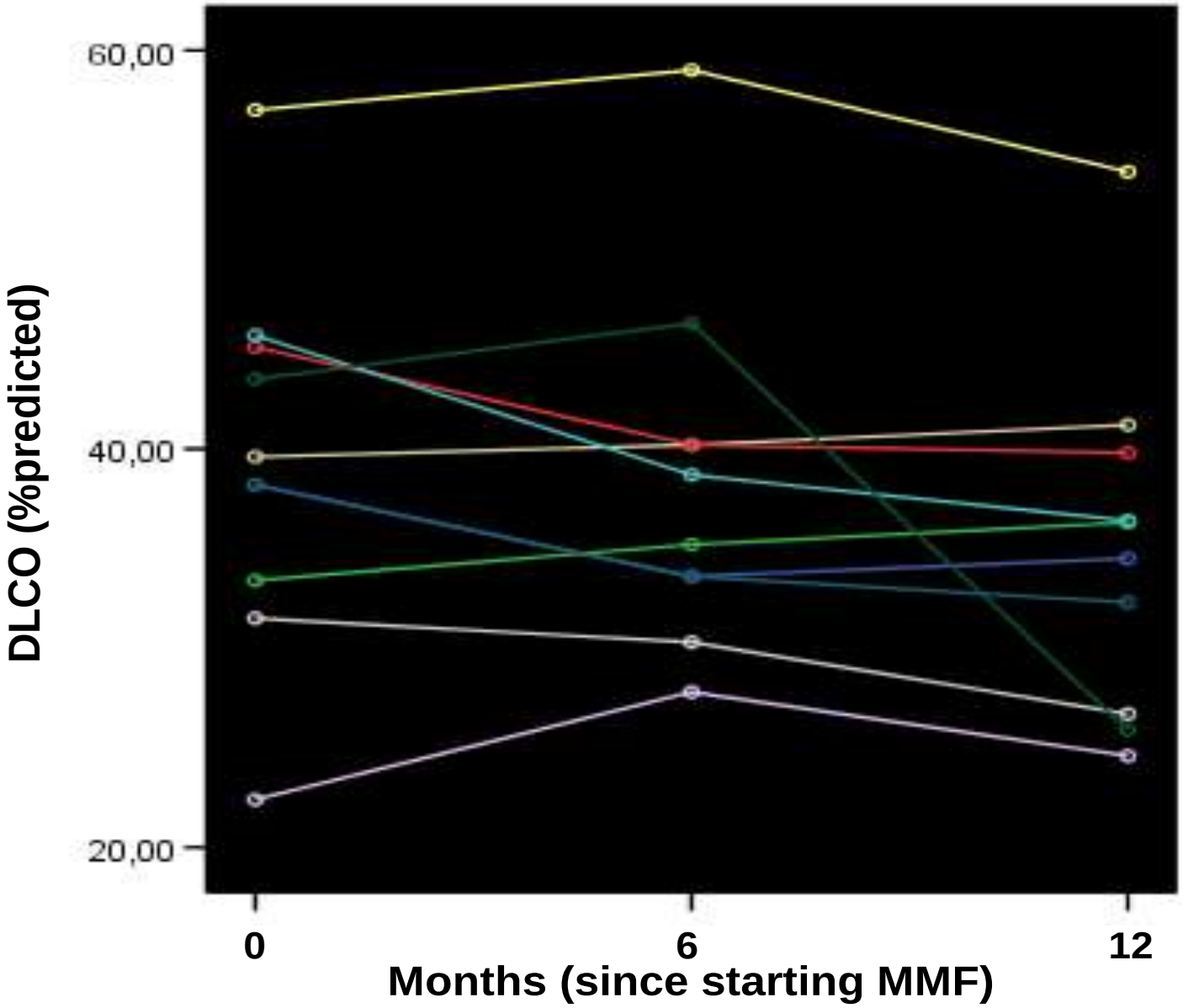

60,00
40,00
20,00
DLCO (%predicted)
0
6
12
Months (since starting MMF)

Figure 3

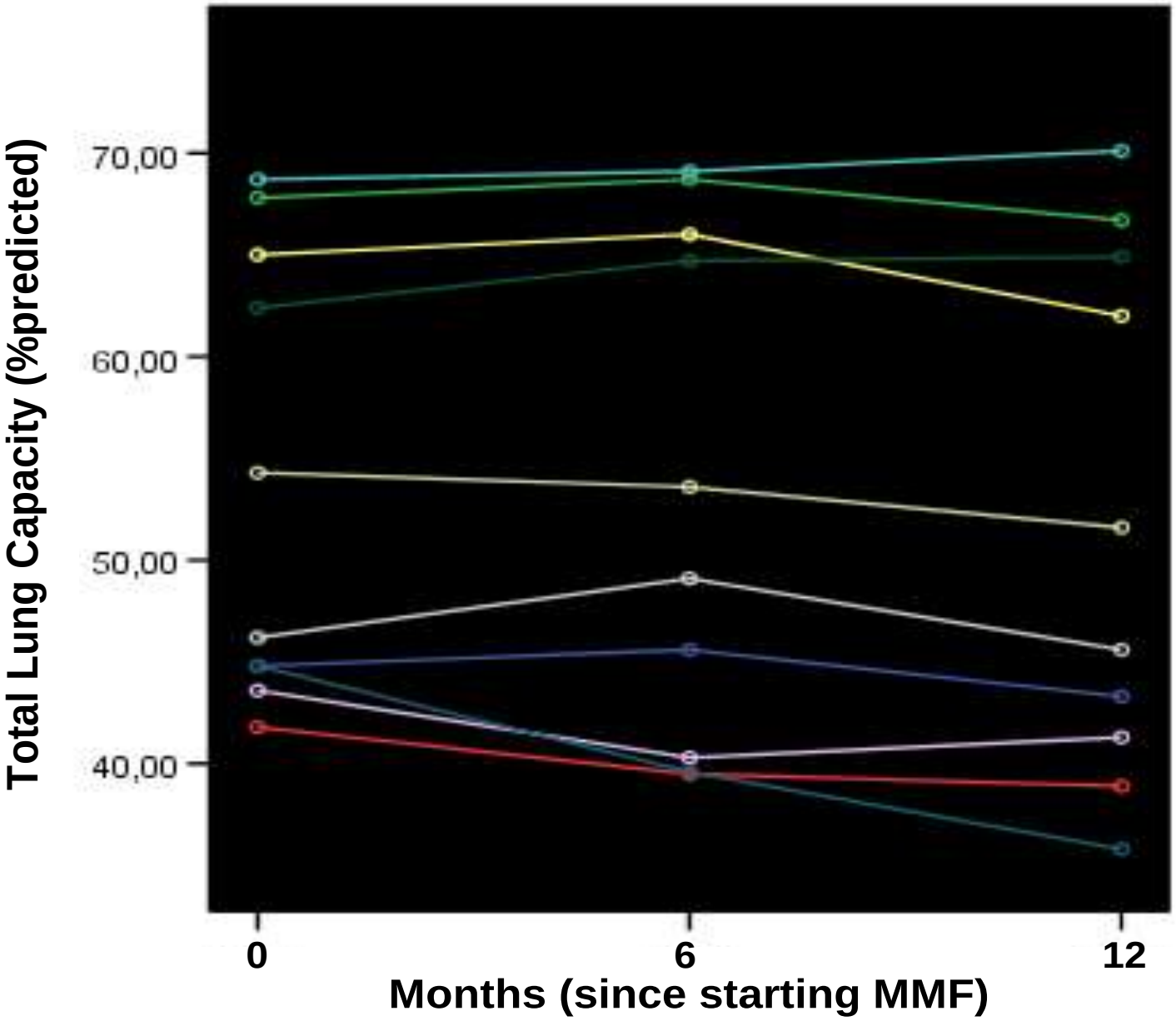

Total Lung Capacity (%predicted)
70,00
60,00
50,00
40,00
0
6
12
Months (since starting MMF)

Figure 4

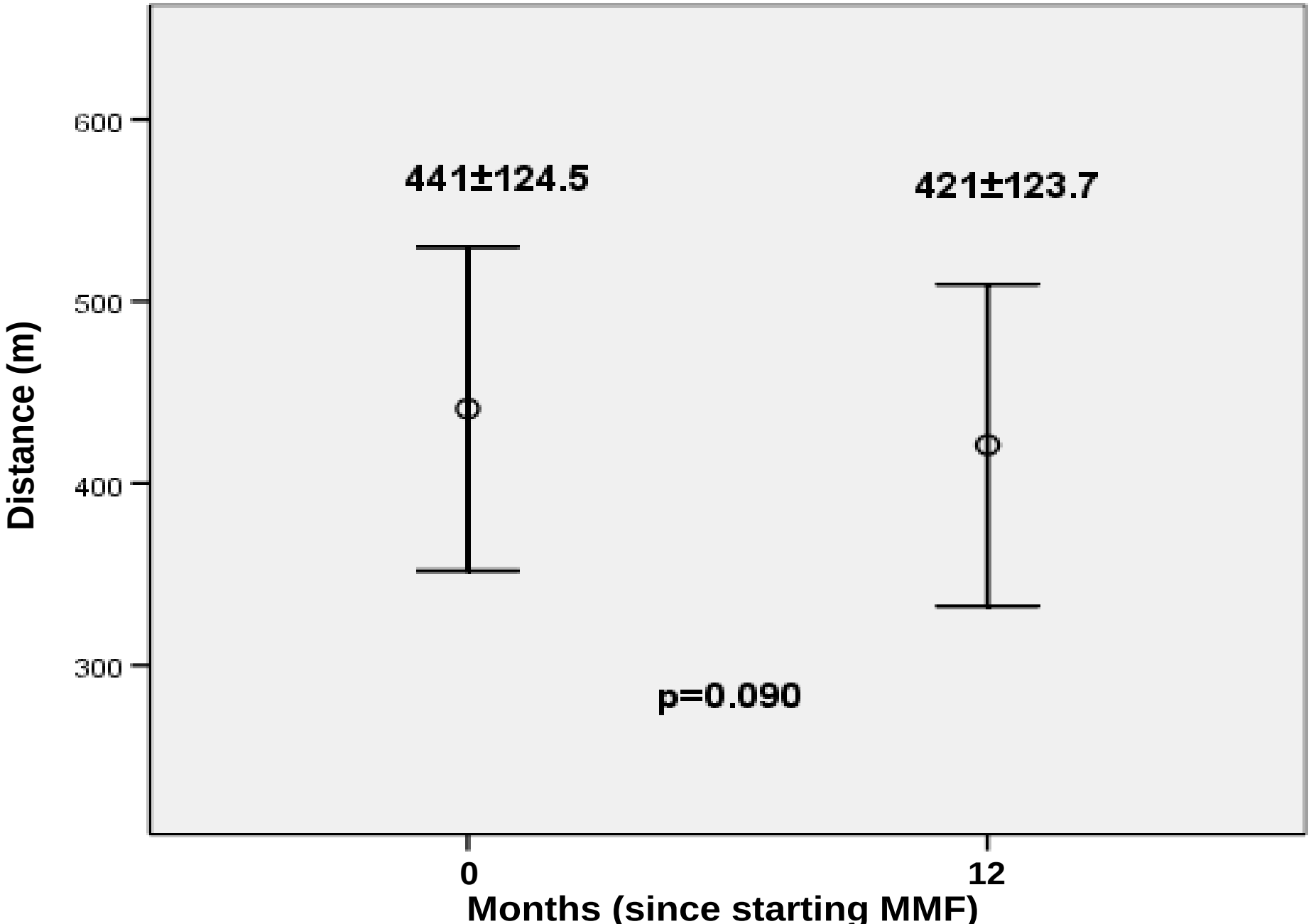
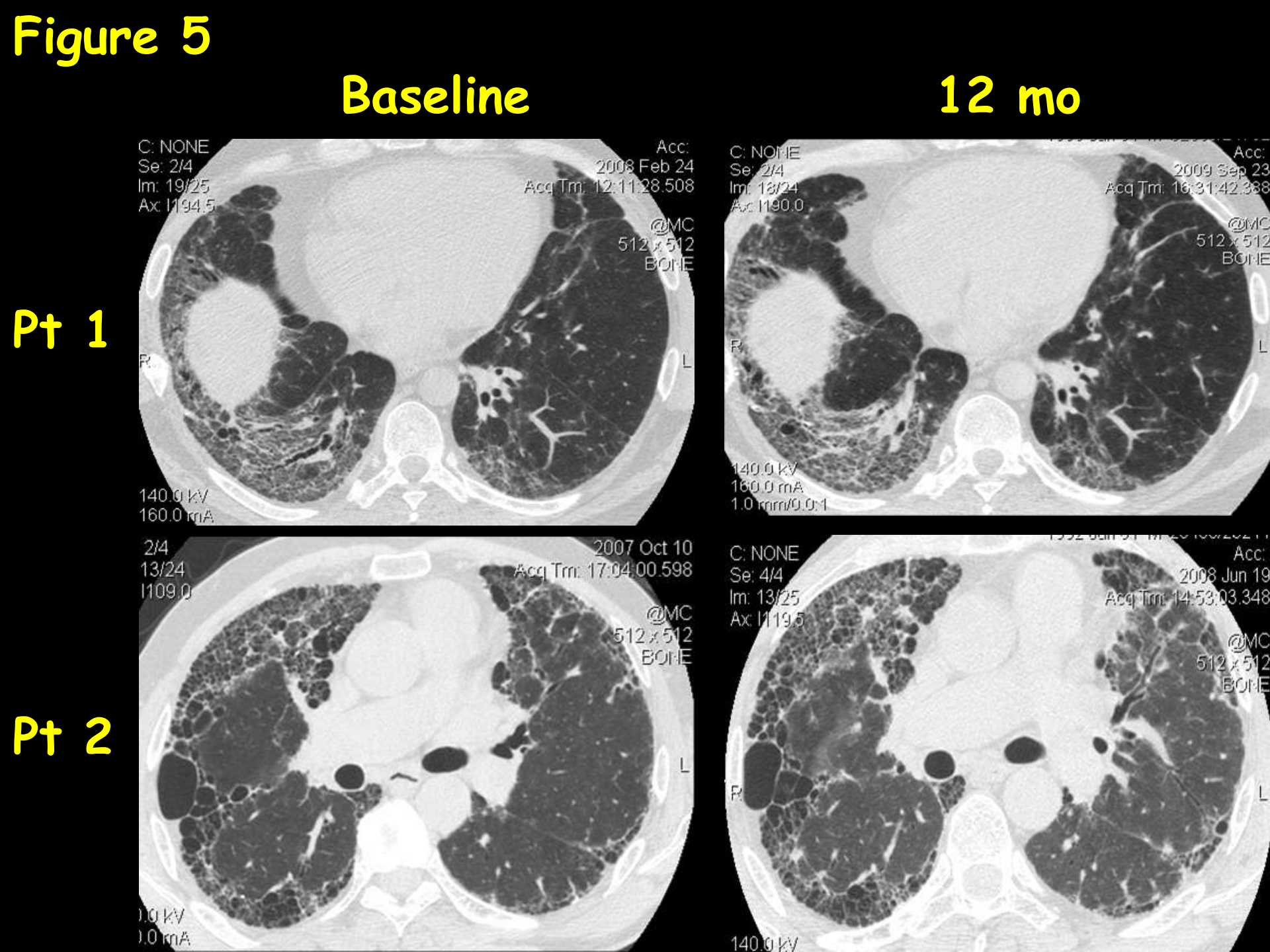

600
500
400
300
Distance (m)
441±124.5
421±123.7
p=0.090
0
12
Months (since starting MMF)

Figure 5


Baseline
12 mo
Pt 1
Pt 2
C: NONE
Se: 2/4
Im: 19/25
Ax: I194.5
Acc:
2008 Feb 24
Acq Tm: 12:11:28.508
@MC
512 x 512
BONE
R
L
140.0 kV
160.0 mA
C: NONE
Se: 2/4
Im: 18/24
Ax: I190.0
Acc:
2009 Sep 23
Acq Tm: 16:31:42.388
@MC
512 x 512
BONE
R
L
140.0 kV
160.0 mA
1.0 mm/0.0:1
2/4
13/24
I109.0
2007 Oct 10
Acq Tm: 17:04:00.598
@MC
512 x 512
BONE
L
C: NONE
Se: 4/4
Im: 13/25
Ax: I119.5
Acc:
2008 Jun 19
Acq Tm: 14:53:03.348
@MC
512 x 512
BONE
R
L
140.0 kV

Conclusions

- Acceptable safety profile
- Disease stabilization based on PFTs
- Deterioration of total disease and GGO extent based on HRCT
- Study Limitation : Retrospective nature + limited number of subjects
- Larger prospective studies are sorely needed

*Altschuler E. Consideration of mycophenolate mofetil for idiopathic pulmonary fibrosis Med Hypotheses 2001