Continuous vs. intermittent inhaled antibiotic therapy in CF

או – הטובים השניים מן האחד?

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Introduction - 1

- The standard of care for chronic PA in CF: inhalation of antibiotics - aerosol mists/ dry powder
- Delivered to the site of lung infection with minimal systemic absorption
- TOBI - 28-day chronic, intermittent regimen (“on/off” regimen)
- Based on the assumption that intermittent use would ↓ resistant bacteria

Introduction - 2

- **BUT** - evidence of ↓LFT and QOL during month off[1,2]
- Emerging strategy of continuous alternating AB – 2 or more
- 2009-2012: use of ≥2 inhaled antibiotic classes more than doubled (CFF Patient Registry); 3 antibiotics – 0.7% (2009) → 3.5% (2012)[3]
- ↑ - continuous anti-bacterial coverage, stable LFTs
- ↓ - treatment burden, cost, AB resistance?
- Historically - continuous inh. colistin, intermittent tobramycin

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[1]Assael et al., J CF 2013
[2]Oermann et al., Ped Pulm 2010
[3]Dasenbrook et al., J CF 2015

Literature Search

- Limited data
- No head-to-head RCT
- Local practices & experience
- No consensus or clear guidelines

Cystic Fibrosis Pulmonary Guidelines

Chronic Medications for Maintenance of Lung Health

Peter J. Mogayzel, Jr.[1], Edward T. Naureckas[2], Karen A. Robinson[3], Gary Mueller[4], Denis Hadjiliadis[5], Jeffrey B. Hoag[6], Lisa Lubsch[7], Leslie Hazle[8], Kathy Sabadosa[8], Bruce Marshall[8], and the Pulmonary Clinical Practice Guidelines Committee*

ARCCM 2013

4. *What is the optimal approach to administration of inhaled antibiotic therapy?* Individuals infected with *P. aeruginosa* typically administer inhaled antibiotics in 28-day, every-other-month cycles. However, it is unknown if this is the best approach for bacterial suppression. For example, as more antibiotics become available, it will be possible to provide continuous therapy by cycling multiple inhaled antibiotics. Studies to determine the optimal approach to initiating and continuing inhaled antibiotics to enhance lung function and minimize bacterial resistance are needed.

Respiratory Medicine (2011) 105 S2, S9-S17

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Aerosolized antibiotic therapy for chronic cystic fibrosis airway infections: continuous or intermittent?

David Lo[a], Donald R. VanDevanter[b], Patrick Flume[c], Alan Smyth[d,*]

- Review – 13 trials (5 intermittent, 8 continuous)
- Intermittent – 1293 patients
- Only 1 study – intermittent vs. continuous; different doses – no direct comparison of safety & efficacy
- Compared to placebo - FEV1↑ (3/5 trials); ↑ time to IV AB; few side effects

- Continuous – 206 patients, longer duration
- Not more adverse events
- AB resistance – no difference (4 trials), to tobi (1 trial), partial resistance (1 trial)
- **Conclusions –**
  - Both regimens are effective
  - Trials of continuous therapy - almost a decade earlier
  - Intermittent antibiotics is less time consuming → improved adherence?
  - If no clinical deterioration during “off” month, patients may not resume treatment

ELSEVIER

Journal of Cystic Fibrosis 15 (2016) 802–808

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

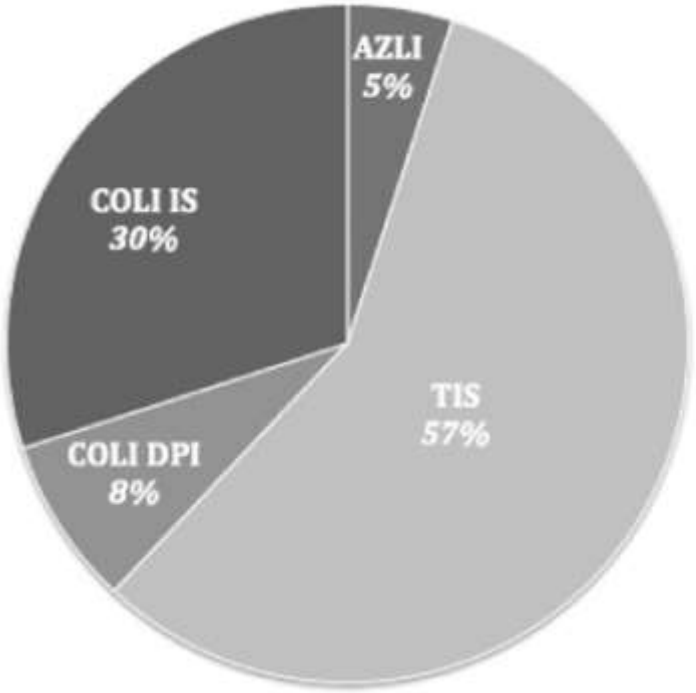
Original Article

Continuous alternating inhaled antibiotic therapy in CF: A single center retrospective analysis

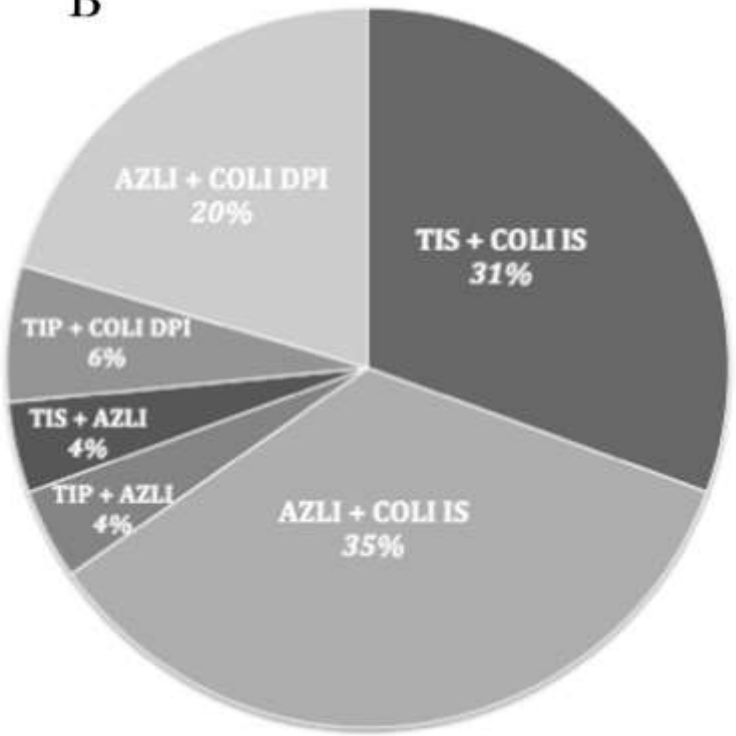
C. Van de Kerkhove [a], P.C. Goeminne [b], M. Kicinski [c], T.S. Nawrot [c], N. Lorent [a], P. Van Bleyenbergh [a], K. De Boeck [d], L.J. Dupont [a,*]

- A retrospective cohort study
- Group 1 (n=49) - initially treated with inhaled antibiotic monotherapy (IAMT), switched to alternated 2 different inhaled antibiotics (CAIT); group 2 (n=40) – IAMT
- The decision to start CAIT – clinical
- FEV1% and number of days on IV antibiotics compared before and after CAIT

A


AZLI
5%
COLI IS
30%
TIS
57%
COLI DPI
8%

B


AZLI + COLI DPI
20%
TIS + COLI IS
31%
TIP + COLI DPI
6%
TIS + AZLI
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TIP + AZLI
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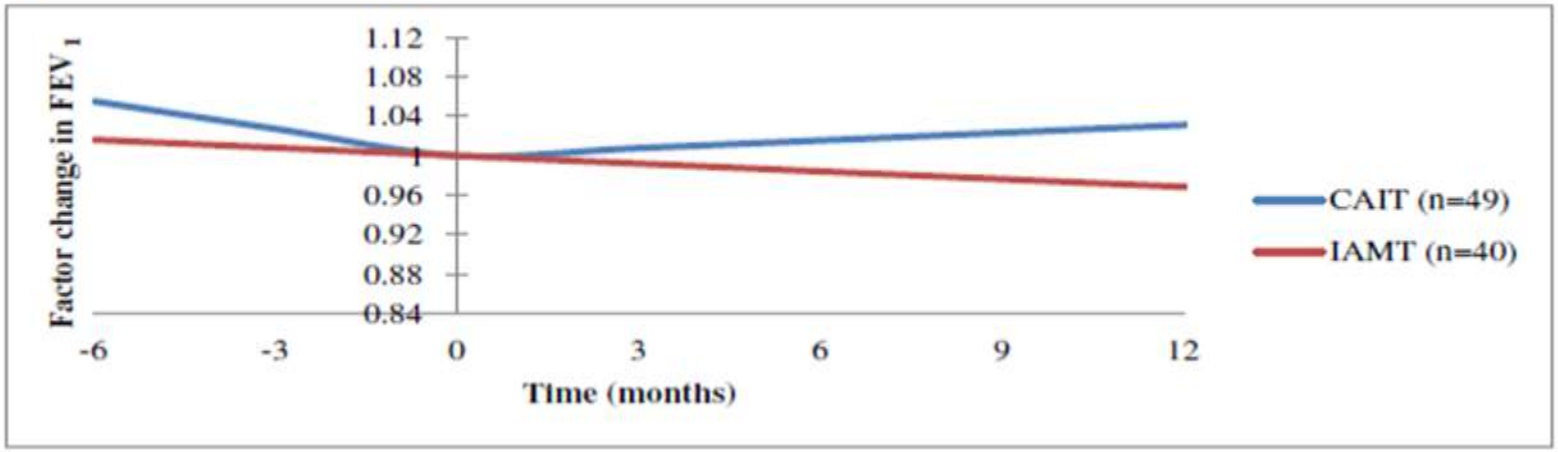
AZLI + COLI IS
35%

A



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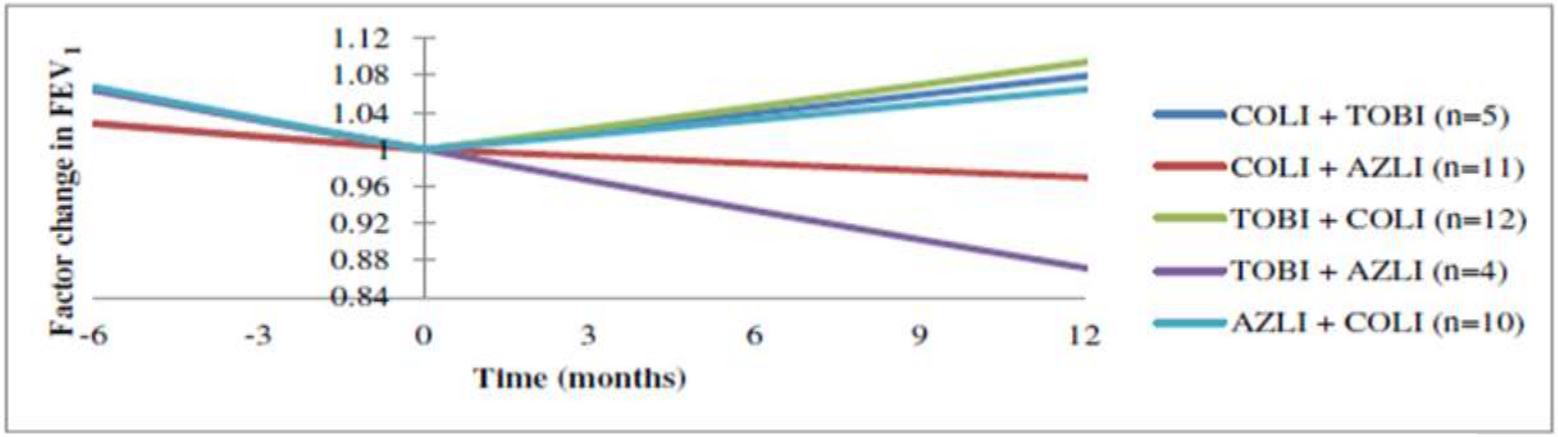

The intervention of CAIT – an improvement factor of 1.148 per year (=1.038/0.904) (95% CI: 1.068–1.236 , p = 0.0002)

Table 2
Effect of adding an additional antibiotic on the evolution of FEV_1.

AB[1]	AB[2]	Evolution during IAMT with AB[1] before CAIT		Evolution during CAIT		Effect of adding additional antibiotic	
		Effect[a]	95% CI	Effect[a]	95% CI	Effect[b]	95% CI
TOBI	+COLI	0.883	0.777–1.003	1.094	0.987–1.213	1.239 *	1.060–1.448
	+AZLI			0.872	0.705–1.078	0.987	0.771–1.264
COLI	+TOBI	0.946	0.835–1.073	1.079	0.927–1.257	1.141	0.947–1.374
	+AZLI			0.969	0.860–1.093	1.025	0.867–1.211
AZLI	+COLI	0.877	0.758–1.016	1.065	0.935–1.212	1.213 *	1.004–1.467

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- No difference of IV AB treatment
- Minor changes in resistance patterns - only 7 (=14%) patients
- Side effects - cough (6 IAMT; 7 CAIT) and bronchospasm (3 IAMT; 4 CAIT)
- **Conclusions –**
  - CAIT - in patients with more severe lung disease ; a small but significant improvement in lung function
  - Effect most pronounced for the addition of COLI to TOBI ($p = 0.0075$)
  - Addition of AZLI to TOBI/COLI - no change in evolution of FEV1

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Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Continuous alternating inhaled antibiotics for chronic pseudomonal infection in cystic fibrosis☆

Patrick A. Flume [a,*], John P. Clancy [b], George Z. Retsch-Bogart [c], D. Elizabeth Tullis [d], Mark Bresnik [c], P. Alex Derchak [e], Sandra A. Lewis [f], Bonnie W. Ramsey [g]

- 45 US CF centers
- Double-blind trial – CAIT vs. intermittent regimen
- 3 cycles of 28-days inhaled AZLI/ placebo X 3/d alternating with 28-days open-label TIS
- Planned enrollment - 250 subjects; did not achieve goal
- 72 patients completed the study (36 in each group)

- 25.7% reduction in exacerbation rate; NS (p = 0.25)
- 26 (55.3%) placebo, 21 (48.8%) AZLI - IV/inhaled antibiotics for PDEs
- Longer time to 1st PDE in AZLI group (175 vs. 140d)
- Difficulties in enrollment –
  - **Increasing use of CAIT as standard care**
  - Introduction of TIP
- **Conclusions –**

  "Although this study was underpowered and did not achieve statistical significance, the results suggest that there may be clinical benefit to continuous alternating treatment"

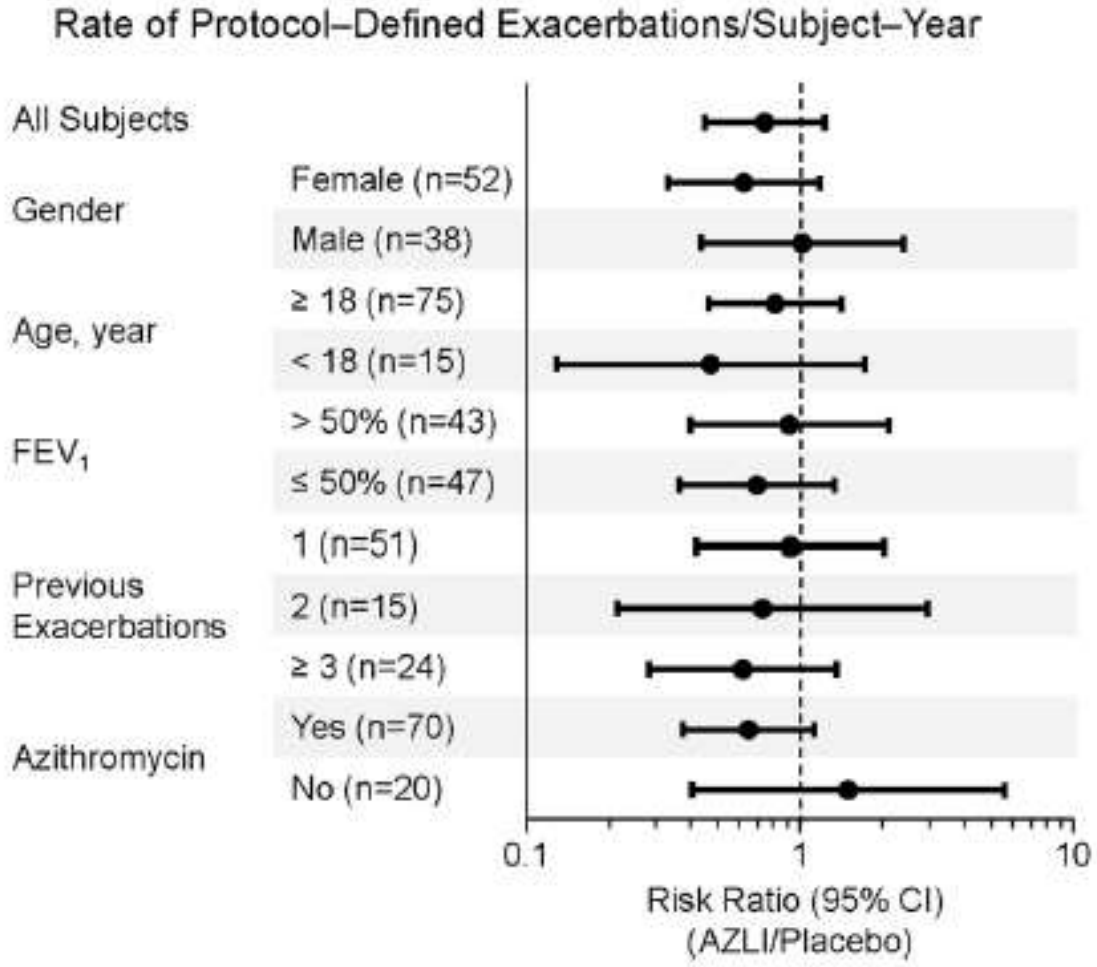

Fig. 2. Rate of protocol-defined exacerbations (primary endpoint) for subgroups of all randomized subjects. Risk ratio = risk of PDE for AZLI-treated subjects/ risk for placebo-treated subjects.

The effect of treatment with intermittent inhaled tobramycin powder on systemic cytokines response in CF patients colonized with Pseudomonas aeruginosa

Michal Gur MD, Yazeed Toukan MD, Fahed Hakim MD, Yuval Geffen PhD, Ronen Bar-Yoseph MD, Vered Nir MD, Lea Bentur MD

* The study was supported by an investigator-initiated grant from Novartis

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Introduction

- Inhaled tobramycin for one month on/one month off – for chronic PA
- TIP™ ↓ time of inhalation
- It is unclear whether laboratory parameters change during the month off period

- **Aim -** to compare spirometry, LCI & circulating inflammatory markers between on/off treatment periods

Methods

- A prospective study; CF patients > 6yrs treated with TIP™
- Spirometry, LCI, sputum, markers of inflammation (blood)
- Evaluations performed before and after 28 days of treatment with TIP™

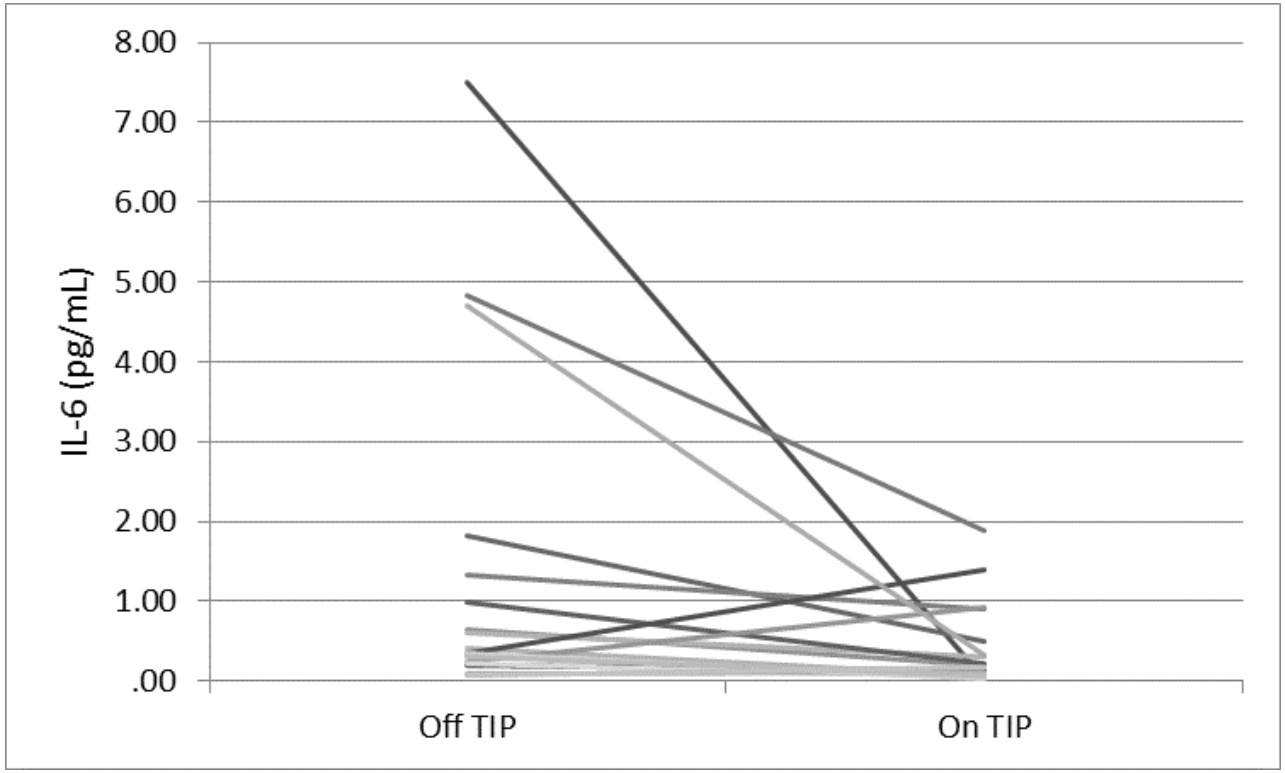
Results - 1

- Nineteen CF patients (10 males); mean age 18.7±9.7 yrs; BMI 19.62±3.53 kg/m2
- After a month off treatment – spirometry & LCI unchanged
- Cultures taken at baseline – PA only in 8 patients; mostly > 1 organism
- **IL-6 ↑ (p=0.022) off treatment**
- No significant change in hs-CRP, IL-8,TNF-α, α1AT and neutrophilic elastase

Results - 2

Parameter	On TIP™	Off TIP™	P value
FEV1 %	75.00 (62.00 - 81.00)	75.00 (64.00 - 82.00)	**0.27**
FEV1 (L)	2.18 (1.30 - 2.60)	2.30 (1.24 - 2.73)	**0.29**
FVC %	83.00 (67.00 - 96.00)	79.00 (73.00 - 98.00)	**0.18**
FVC (L)	2.55 (1.89 - 3.20)	2.75 (1.93 - 3.53)	**0.19**
FEF25-75 %	39 (66-81)	39 (68-84)	**0.41**
FEF25-75 (L)	2.36 (1.19-3.18)	2.2 (1.1-3.3)	**0.38**
LCI %	152.00 (131.00- 231.50)	152.00 (139.00 - 193.00)	**0.35**
LCI	8.48 (7.43 - 13.15)	8.71 (7.88 - 11.35)	**0.33**
hs-CRP (n=14)	4.59 (2.94-13.60)	5.28 (2.84-12.9)	**0.57**
IL-6 (pg/mL)	0.19 (0.07-0.7)	0.41 (0.23 - 1.57)	**0.02**
IL-8 (pg/mL)	3.82 (2.41-7.83)	5.10 (2.60 - 13.70)	**0.12**
TNF-α (pg/mL)	7.38 (5.56-22.50)	11.56 (6.17 - 18.59)	**0.62**
α1AT (mg/dL)	1.98 (0.63 - 4.23)	1.17 (0.56 - 4.10)	**0.14**
Neutrophilic elastase	27.62 (23.73-30.33)	23.93 (18.47-27.9)	**0.17**

Results - 3



Conclusions

- The results support the relative stability of CF patients during the month off therapy
- The difference in serum IL-6 – possibly ↑ inflammation off therapy; small numbers preclude further conclusions
- **Enrollment was limited because of the evolving practices of a continuous alternating regimen**
- Larger multicenter studies are needed to assess the on/off strategy
- The best regimen, combination & number of AB – yet to be determined

אצלי – אין ספק שהשניים טובים...

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או שאולי 3 נה ה- 2 התרשים?

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