

**Falk Symposium
Immunoregulation in Inflammatory Bowel
Diseases - Current Understanding and Innovation
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Apheresis for the Treatment of IBD



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History of Apheresis in IBD

	Method	Disease	Efficacy
1985 Bicks et al.	Centrifugation	CD	4/7
1995 Sawada et al.	Cellsorba®	UC CD	UC; 21/25, CD; 16/19
1996 Rembacken et al.	Adacolumn®	UC CD	UC; 9/14, CD; 5/6



Widespread use in Japan and EU

Evidence-Based Clinical Efficacy of Cytapheresis in UC

Granulocyte And Monocyte Adsorption Apheresis

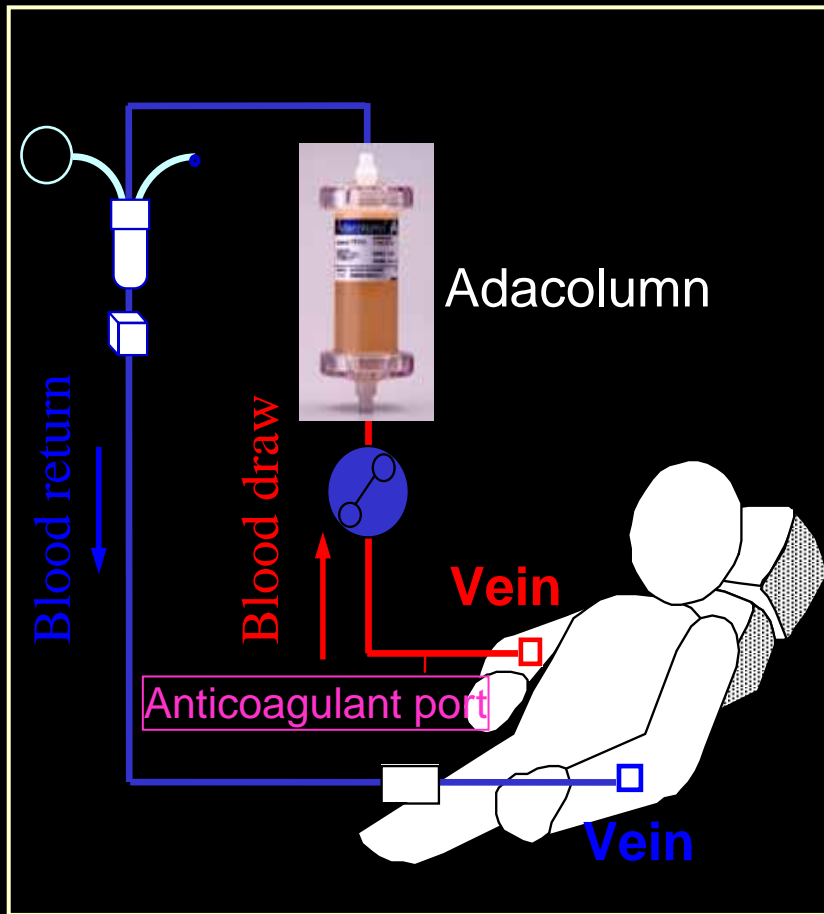
(GCAP)

- Multicenter randomized controlled trial between GCAP and steroids (Shimoyama et al: Japanese J Apheresis 18: 117, 1999)
- GCAP for steroid-resistant UC by prospective pilot study (Hanai et al: Cin Gastroenterol Hep 1: 28, 2003)
- GCAP is useful as an alternative therapy in steroid-dependent UC (Naganuma et al: Inflamm Bowel Dis 10: 251, 2004)

Leukocytapheresis (LCAP)

- Multicenter randomized controlled trial between LCAP and high-dose prednisolone (Sawada et al. Curr Pharm Des 9: 307, 2003)
- LCAP in UC: A multicenter double-blind prospective case-control study with sham apheresis as placebo treatment (Sawada et al. Am J Gastroenterol 100: 1362, 2005)

Scheme of Adacolumn® Treatment



Duration: 60 minutes
Flow Rate: 30mL/minutes.
Anticoagulant: Heparin

Mechanisms of Actions: Immunomodulation 1

-Changes in granulocytes function associated with apheresis-

The expression of L-selectin and the adhesion to HUVEC (endothelial cells)

were reduced by apheresis procedure

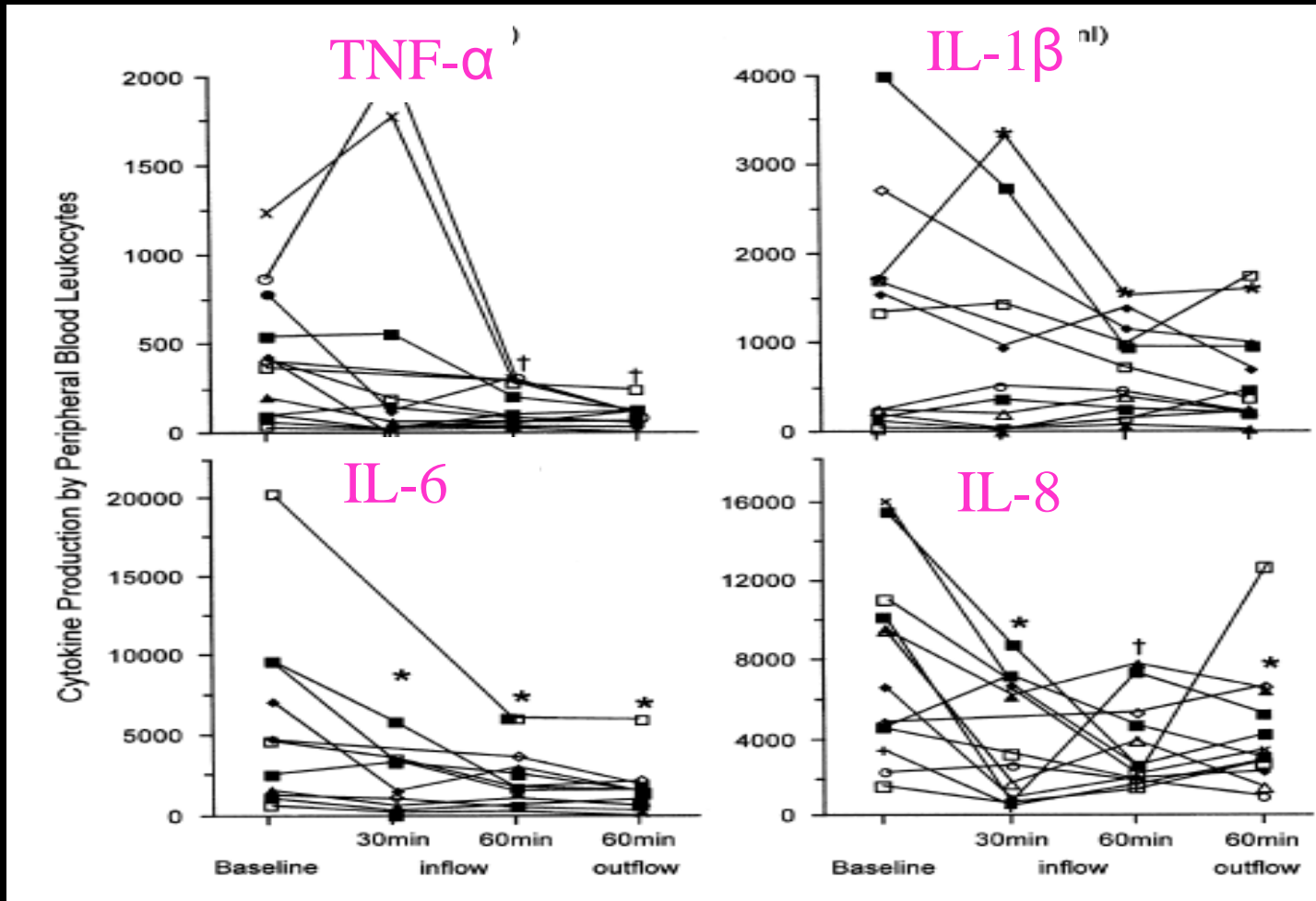
Condition	Adhesion molecule (n = 26) Mean fluorescence intensity		% adhesion to HUVEC (n = 7)	% phagocytic granulocytes (n = 9)
	L-selectin	Mac-1		
Preapheresis	4.17 (1.82-11.17)	8.89 (4.91-24.64)	28.9 (12.9-51.4)	87.3 (65.3-92.5)
Postapheresis	2.00 (1.22-4.68)	25.36 (17.09-50.35)	9.9 (5.7-16.3)	87.0 (71.3-90.3)
p value ^a	p < 0.0001	p < 0.0001	p < 0.02	N.S.

Subjects: Patients with Rheumatoid Arthritis

Kashiwagi N, et al. Therapeutic Apheresis 1998; 2: 134-141.

Mechanisms of Actions: Immunomodulation 2

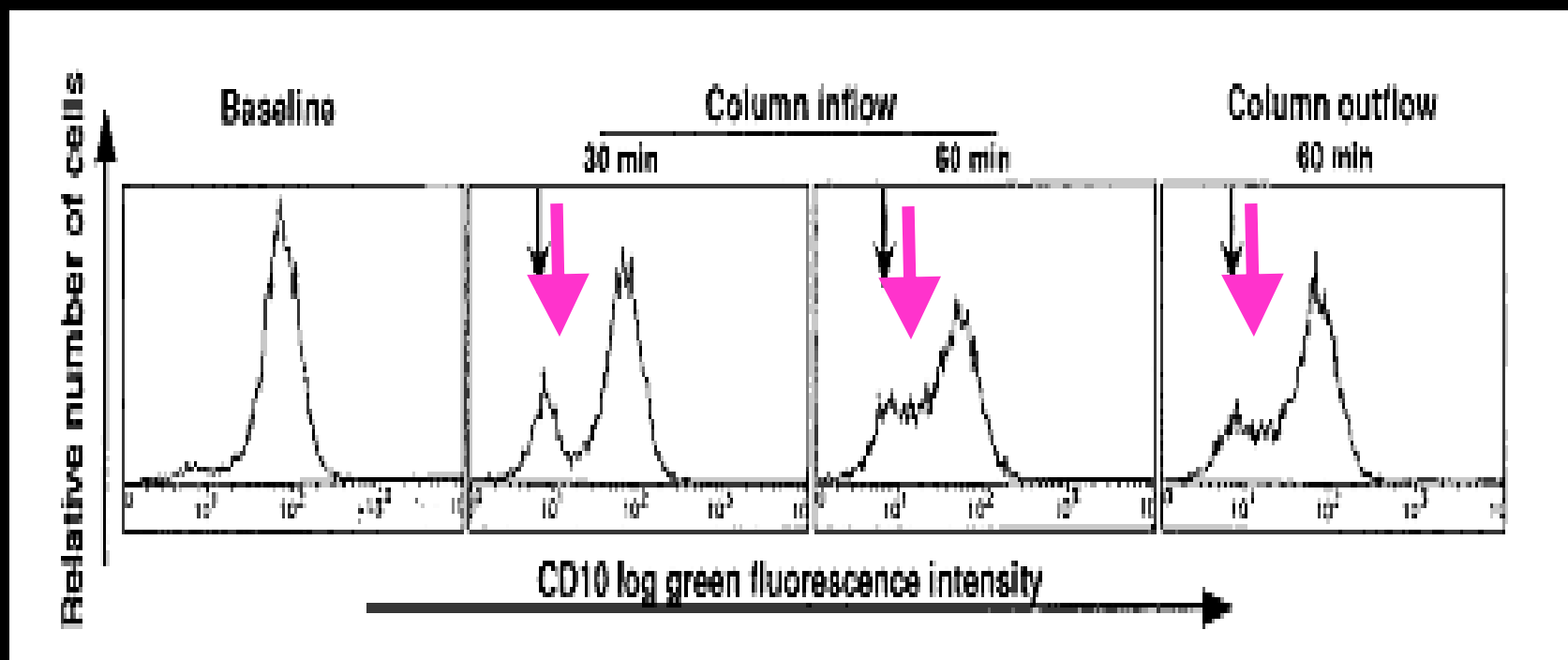
Suppression of pro-inflammatory cytokines TNF- α , IL-1 β , IL-6 and IL-8 produced by blood leucocytes during Adacolumn



Shimoyama T et al. *J Clin Apheresis*. 2001;16:1-9.

Mechanisms of Actions: Immunomodulation 3

Decrease of CD10⁺ Neutrophils and emergence of CD10⁻ Neutrophils (naive) during Adacolumn therapy



Kashiwagi N, et al. Dig Dis Sci 2002;47:2349-53

Efficacy of Adacolumn compared to Prednisolone

A Multi-center, Randomized, Clinical Trial in Patients with Active Ulcerative Colitis (UC)

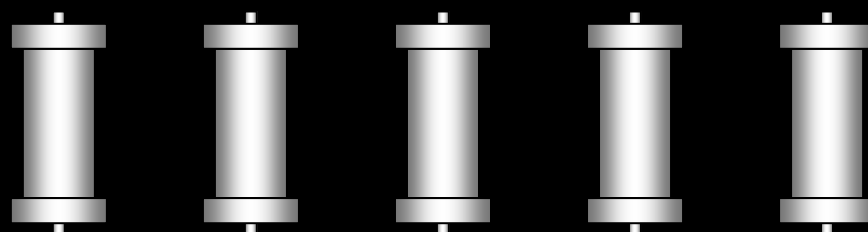
Subjects: 120 with moderately to severely active UC

Randomly divided into Adacolumn group or high dose Prednisolone group

Prednisolone



Adacolumn



x1 / week

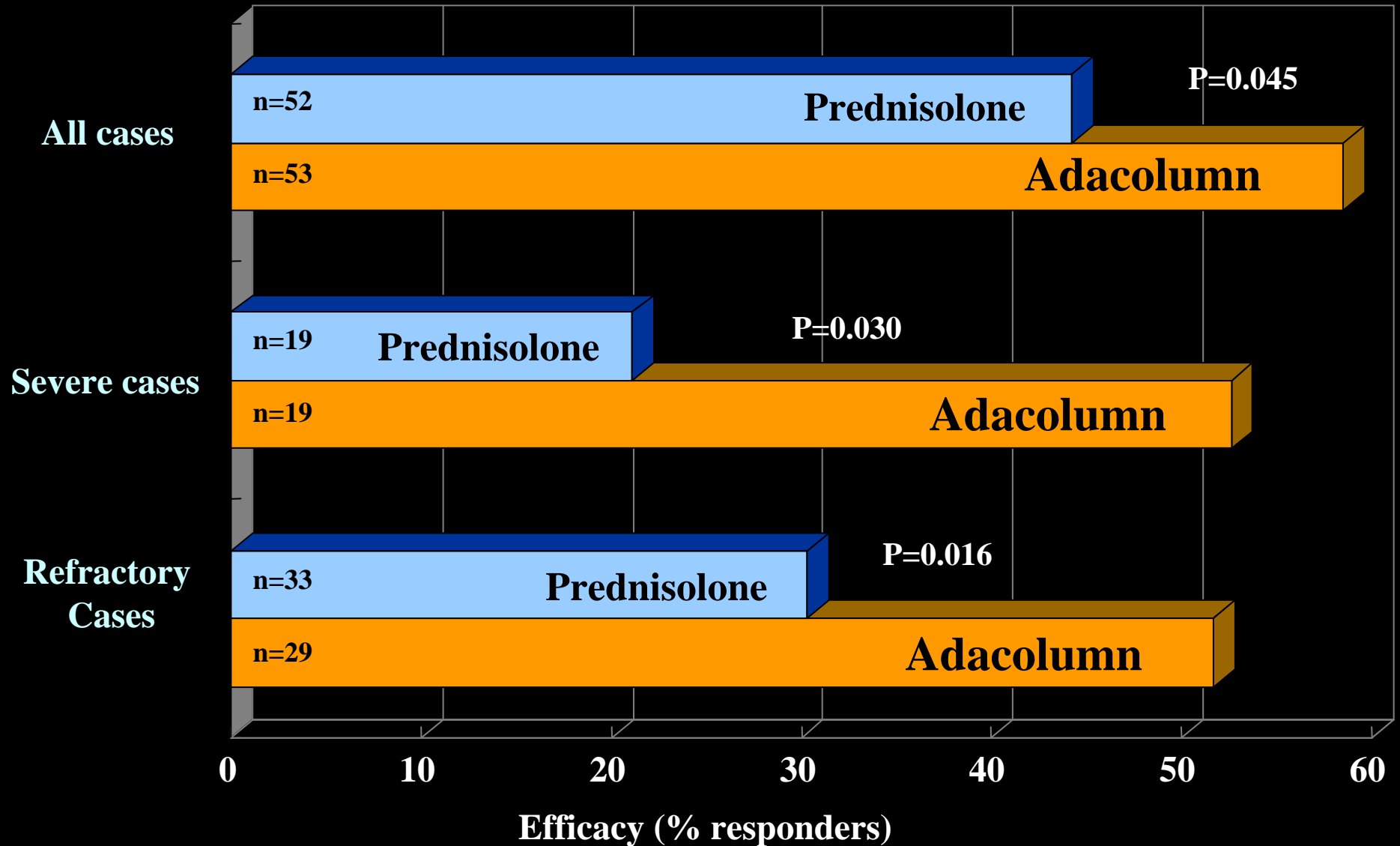


week 7

overall assessment

Shimoyama T, et al. Jpn J Apher 1999; 18: 117-131.

Clinical Efficacy of Adacolumn vs Prednisolone



Shimoyama T, et al. *Jpn J Apher* 1999; 18: 117-131.

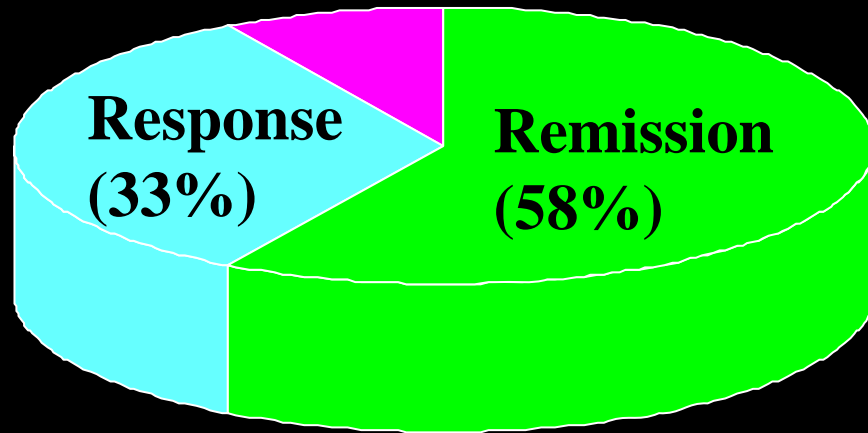
Types and Frequencies of Adverse Reactions

	Adacolumn (n=59)	Prednisolone (n=59)
Circulatory and respiratory organs	Headache	1
	Dizziness on standing	1
	Dizziness	1
Digestive organs	Nausea	1
	Duodenal perforation	1
Hypersensitivity	Fever	2
	Flushing	2
Liver dysfunction	mild	4
	moderate	2
Musculoskeletal symptoms	Osteoporosis	3
	Reduced bone mass	3
	Compressed fracture of lumbar vertebra	2
Lipid and protein metabolism disorders	Moon face	10
	Hypoproteinaemia	2
	Hypercholesterolaemia	1
Dermatological disorders	Acne	5
	Pyoderma gangrenosum	1
Others		6
Total adverse events (Pts)	5/59 (8.5%)	27/59 (45.8%)

Shimoyama T, et al. Jpn J Apher 1999; 18: 117-131.

GCAP Is Effective for Steroid-Dependent UC

Non-response (8%)

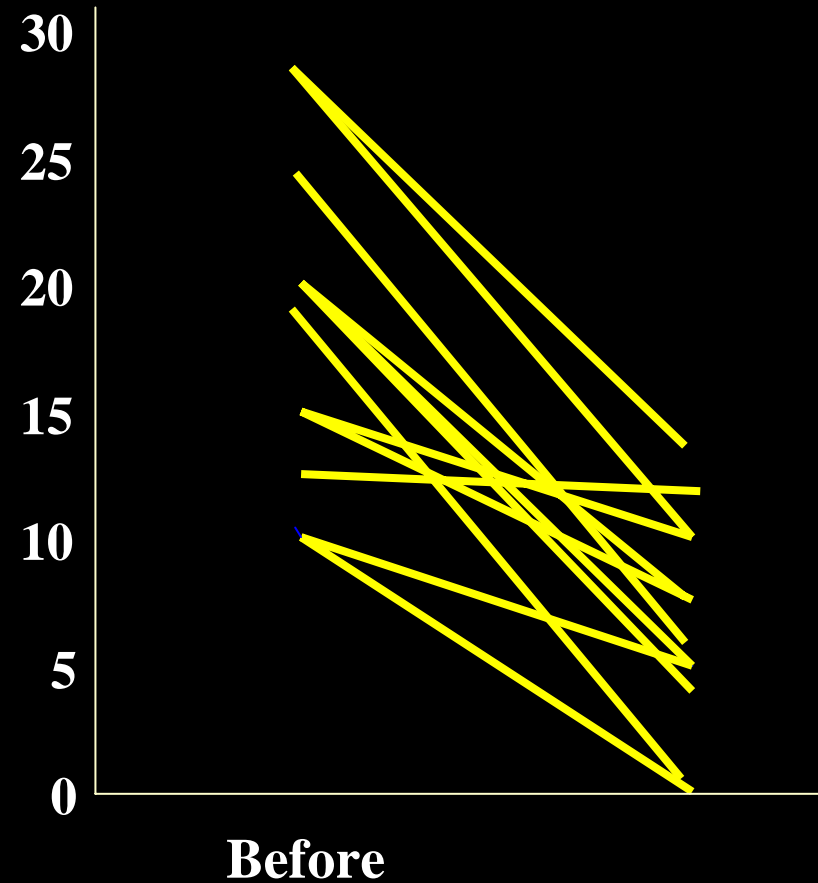


Before



After

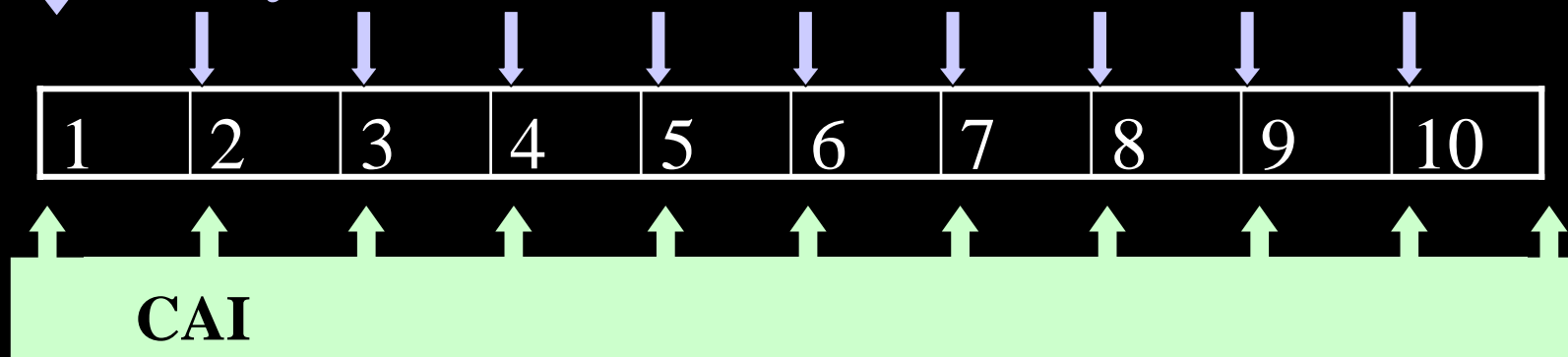
Steroid-Tapering Effect (mg/day)



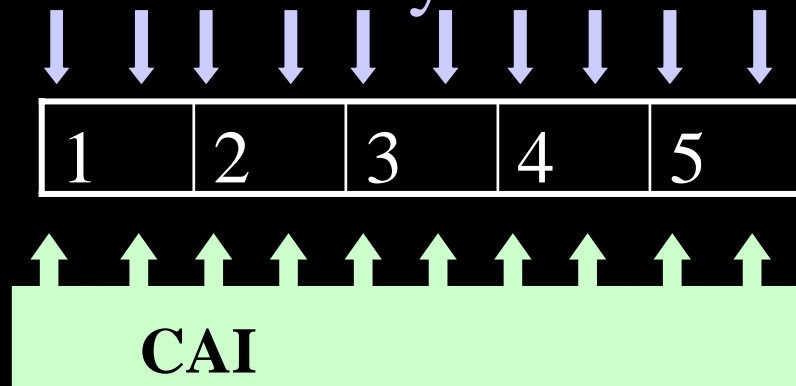
Efficacy of Intensive Adacolumn Treatment

A Multicenter, Prospective, Randomized, Controlled
Trial Between Weekly And Semiweekly Treatment
With Adacolumn For Active UC

Weekly Adacolumn (n=45)



Semiweekly Adacolumn (n=52)



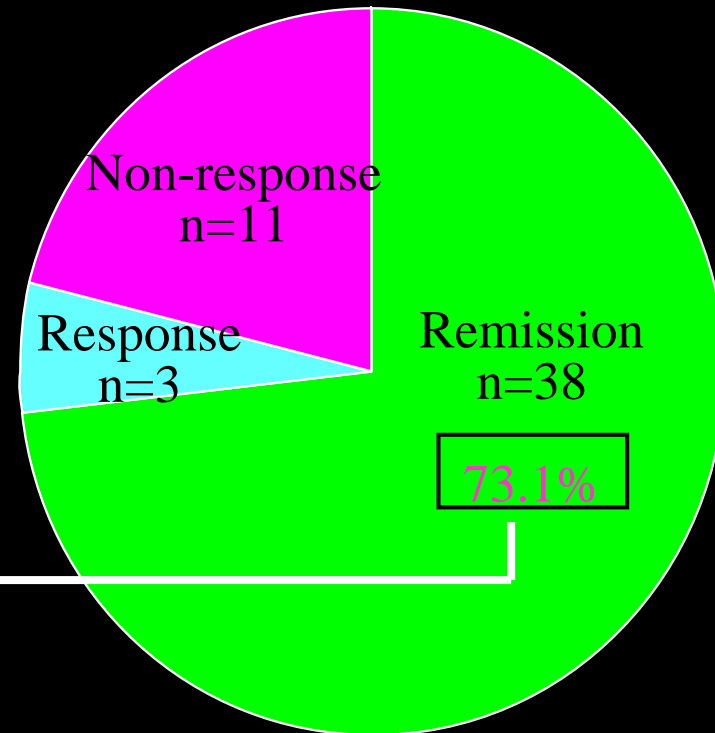
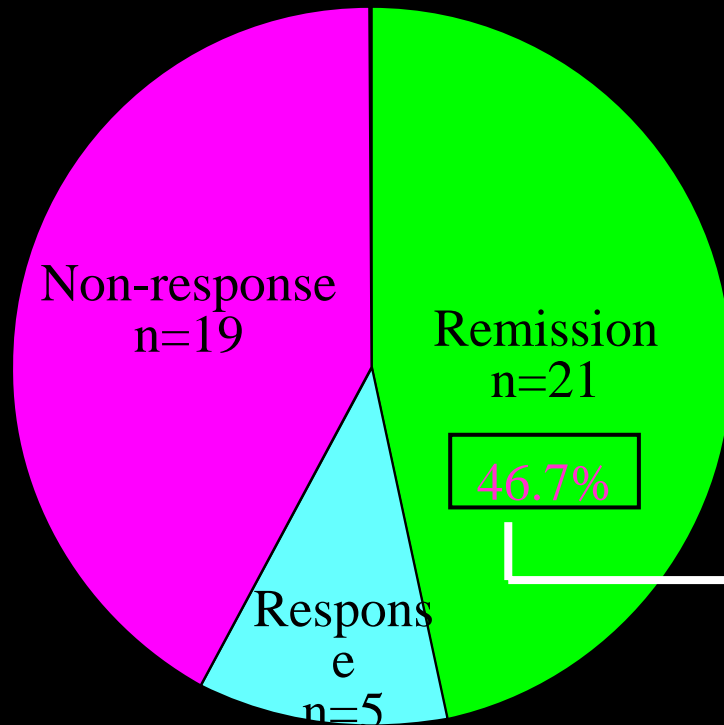
Sakuraba A, Hibi T et al. 2005 UEGW

An Interim Report of Multicenter, Prospective, Randomized Controlled Trial between Weekly and Semiweekly Treatment with GCAP

Weekly (n=45)

Rate of Inducing Remission

Semiweekly (n=52)



P=0.012

Days for Inducing Remission

Weekly

28.1 days

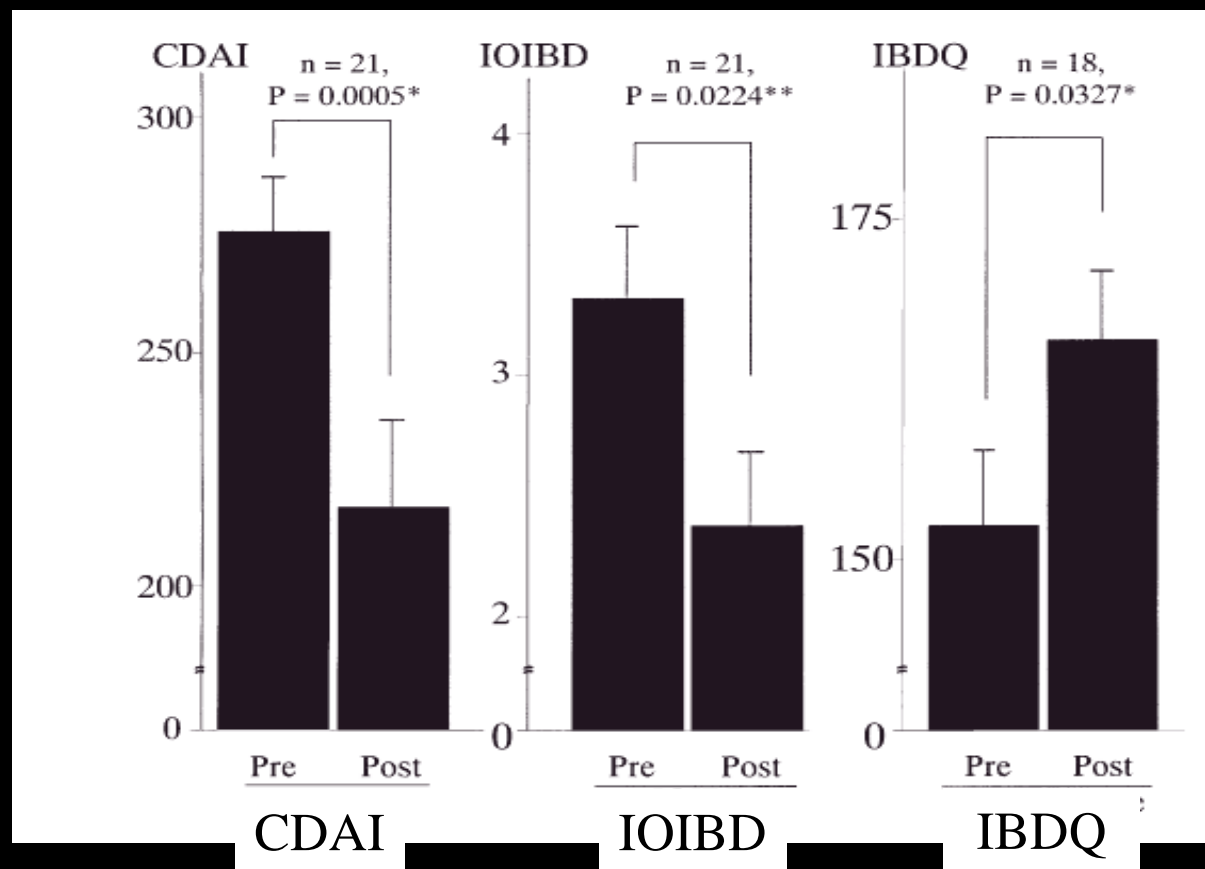
Semiweekly

15.9 days

P=0.0002

Adacolumn apheresis for refractory Crohn's disease

An Open-labelled, Multicenter, Prospective, Unblinded Study

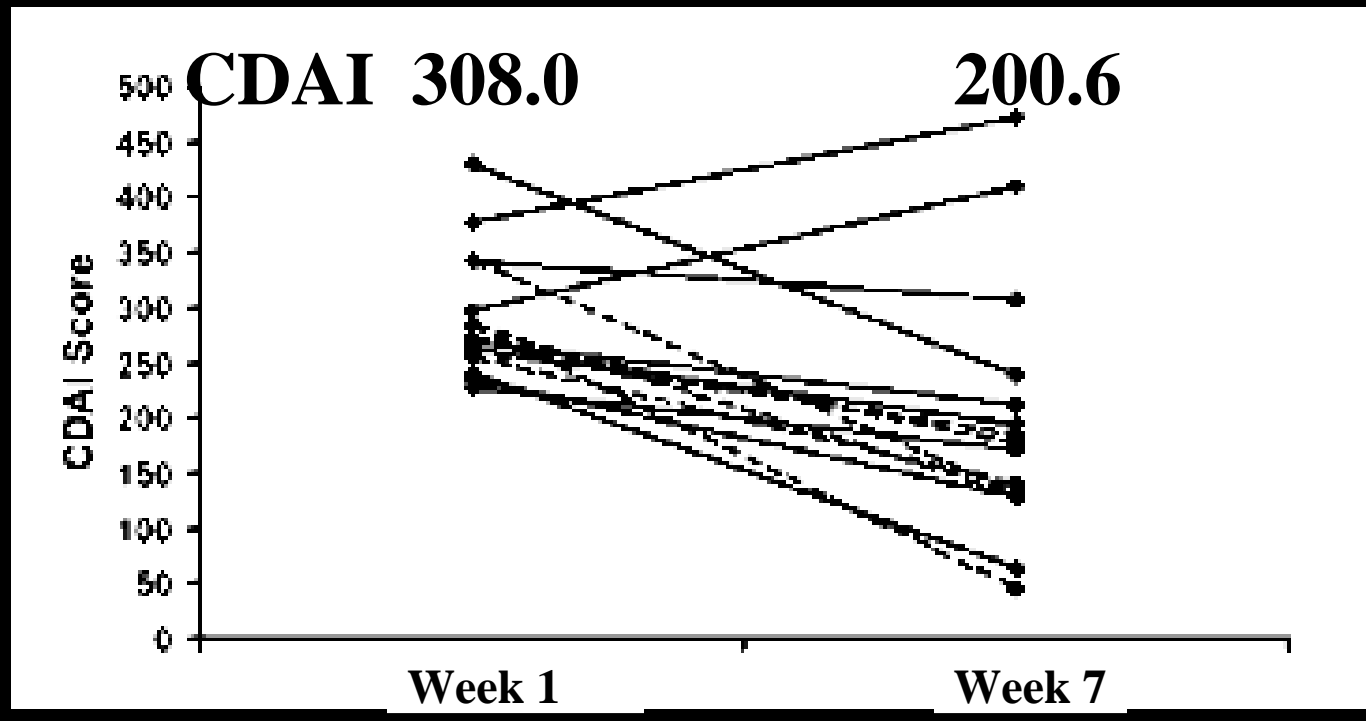


Subjects: 21 CD patients refractory to 5-ASA, steroids etc.
Efficacy: 11/21 (52.4%)
Remission: 6/21 (27.0%)

Fukuda Y, Hibi T et al. J Gastroenterol. 2004;39:1158-64.

Efficacy of Adacolumn in Crohn's disease

An US Pilot, Open-labelled, Multicenter, uncontrolled Trial



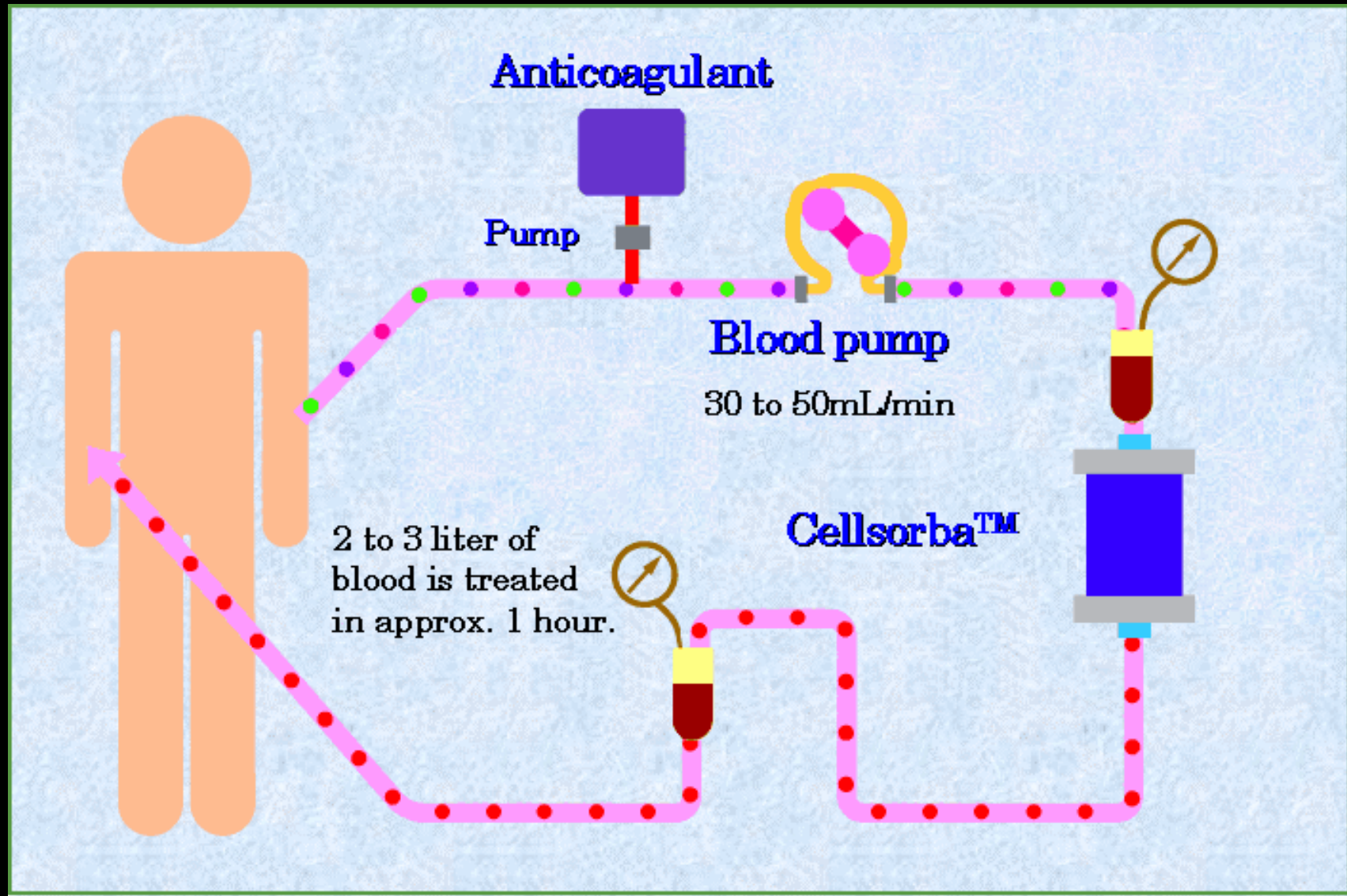
Subjects: 15 moderate to severe CD patients refractory to conventional medication

Response: 9/15 (60%)

Remission: 6/15 (40%)

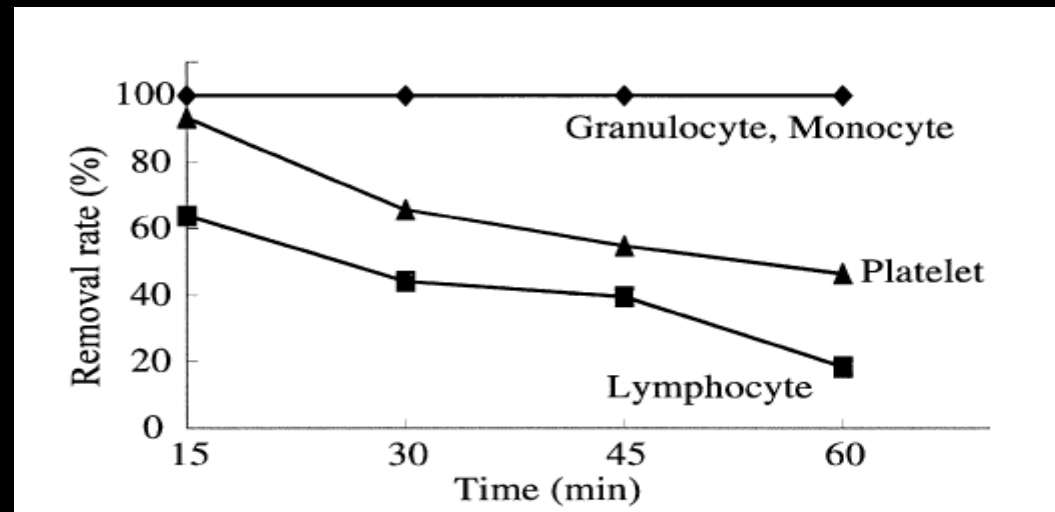
Sands BE, Sandborn WJ et al. American College of Gastroenterology, Annual Scientific Meeting; 2004.

Scheme of Celsorba Treatment

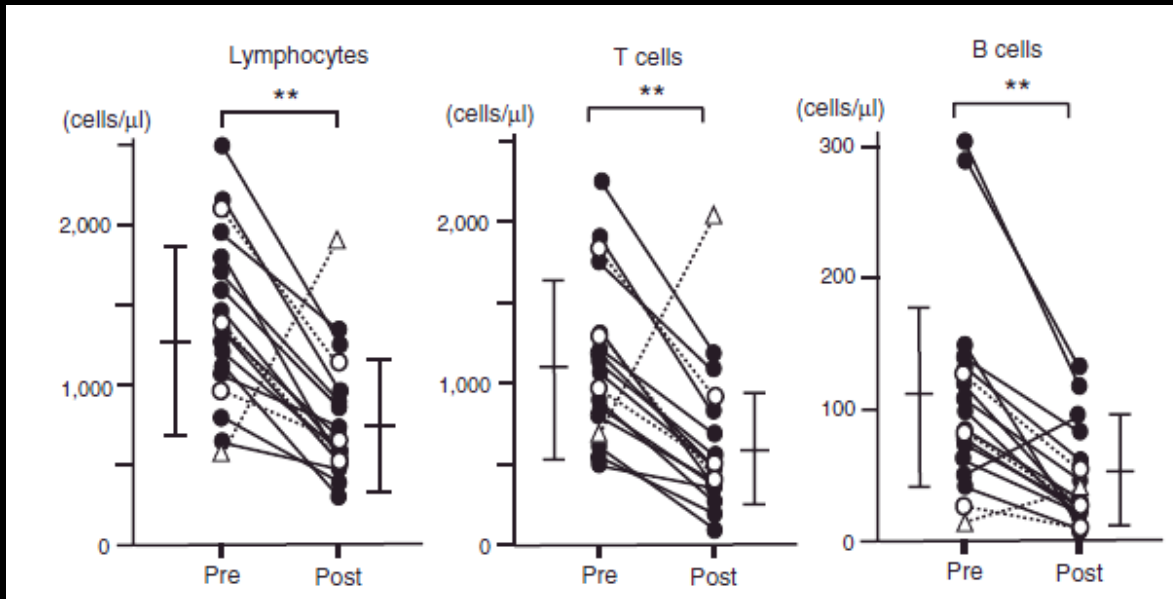


Blood Cell Adsorption Efficiency of Cellsorba

	Number of cells adsorbed ($\times 10^9$)	Adsorption efficacy (%)
Granulocytes	11.0	95
Monocytes	0.52	100
Lymphocytes	2.0	85
Platelets	520	55

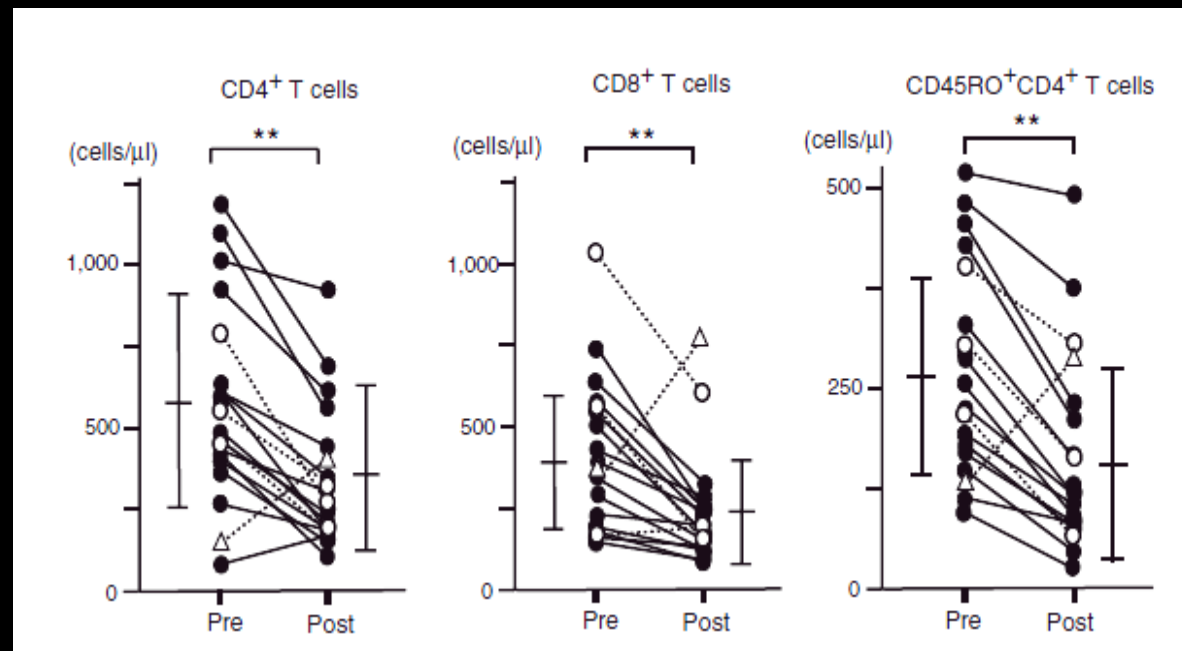


Mechanism of Action: Immunomodulation 1



Decrease in the number of lymphocytes, T and B cells after Cellsorba therapy

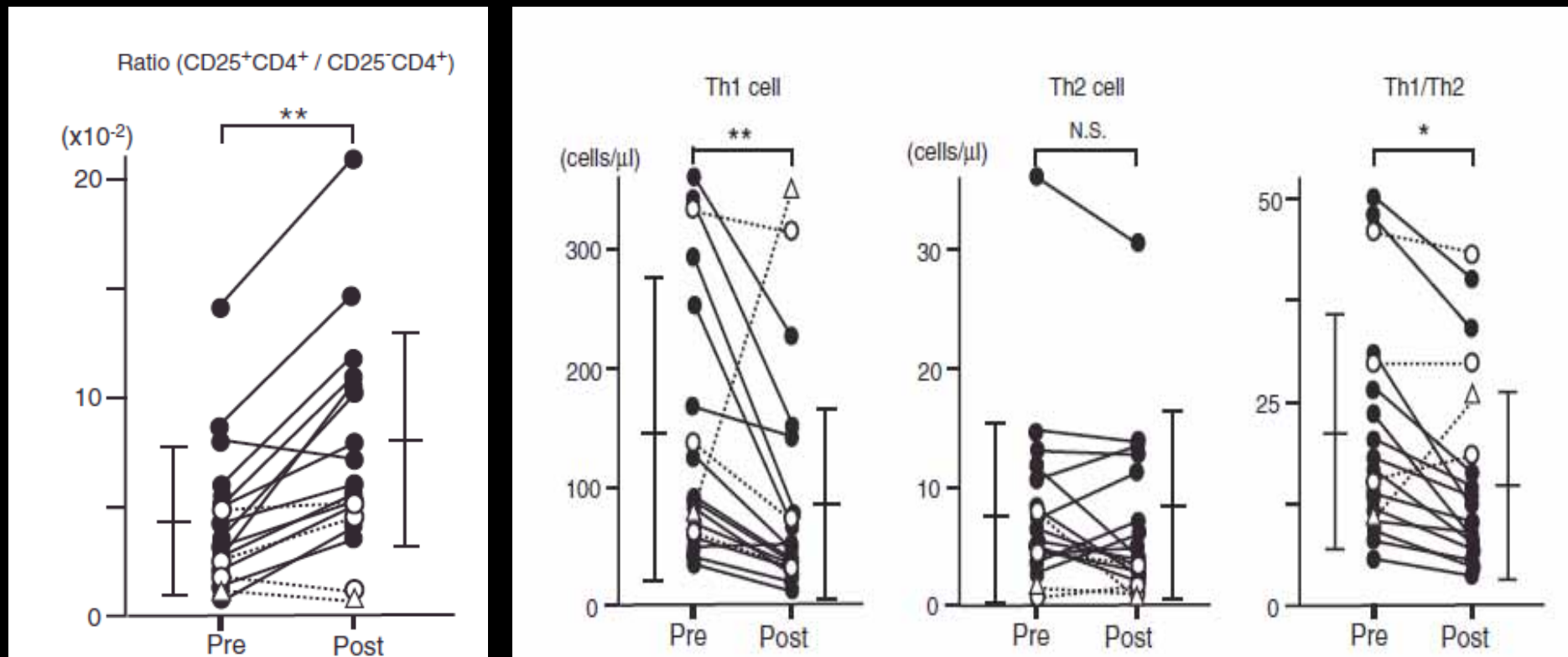
Decrease in the number of CD4+, CD8+ and CD45RO+CD4+ T cells after Cellsorba therapy



Mechanism of Action : Immunomodulation 2

An Increase in the ratio of regulatory T cells/effector T cells

A reduction in the ratio of Th1(IFN- γ)/Th2(IL-4) T cells



Andoh A et al. Therapeutic Apheresis and Dialysis; 2005; 9;270-276.

Efficacy of CellSORBA compared to High-dose Prednisolone

A Multicenter, Prospective, Unblinded Trial

Subjects: 76 Moderate to Severe UC patients

Randomly divided to high-dose Prednisolone group or
CellSORBA group

Sawada K, Shimoyama T et al. Curr Pharm Des 9: 307, 2003

High Prednisolone (h-PSL) group

Study starts.

Increase steroid dose 30-80mg/day

Steroid (prednisolone)

3.0 ~ 4.0 g/day of SASP or 1.5 ~ 2.0 g/day of 5-ASA

TIME

Leukocytapheresis (Cellsorba) group

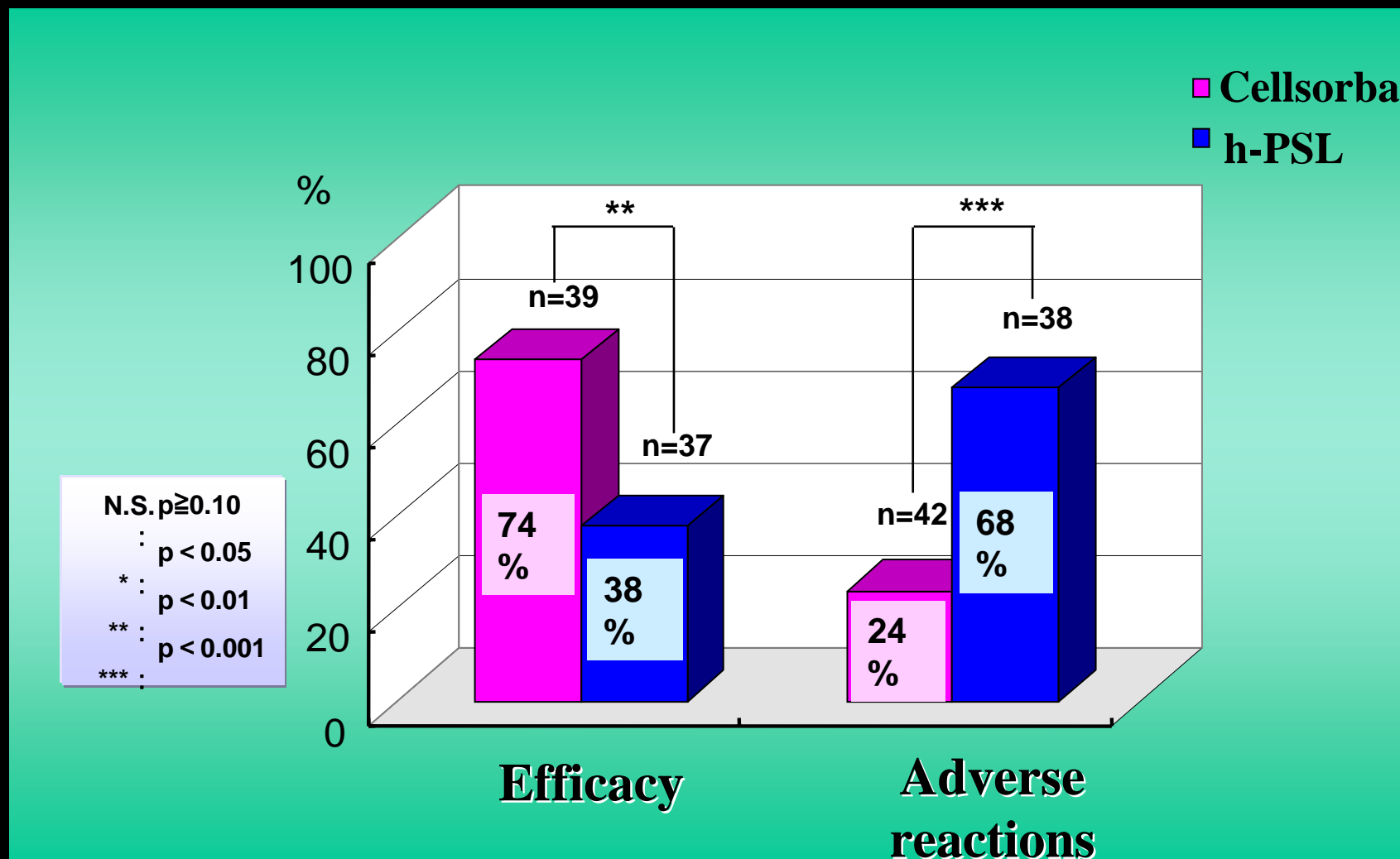
Study starts.

Cellsorba

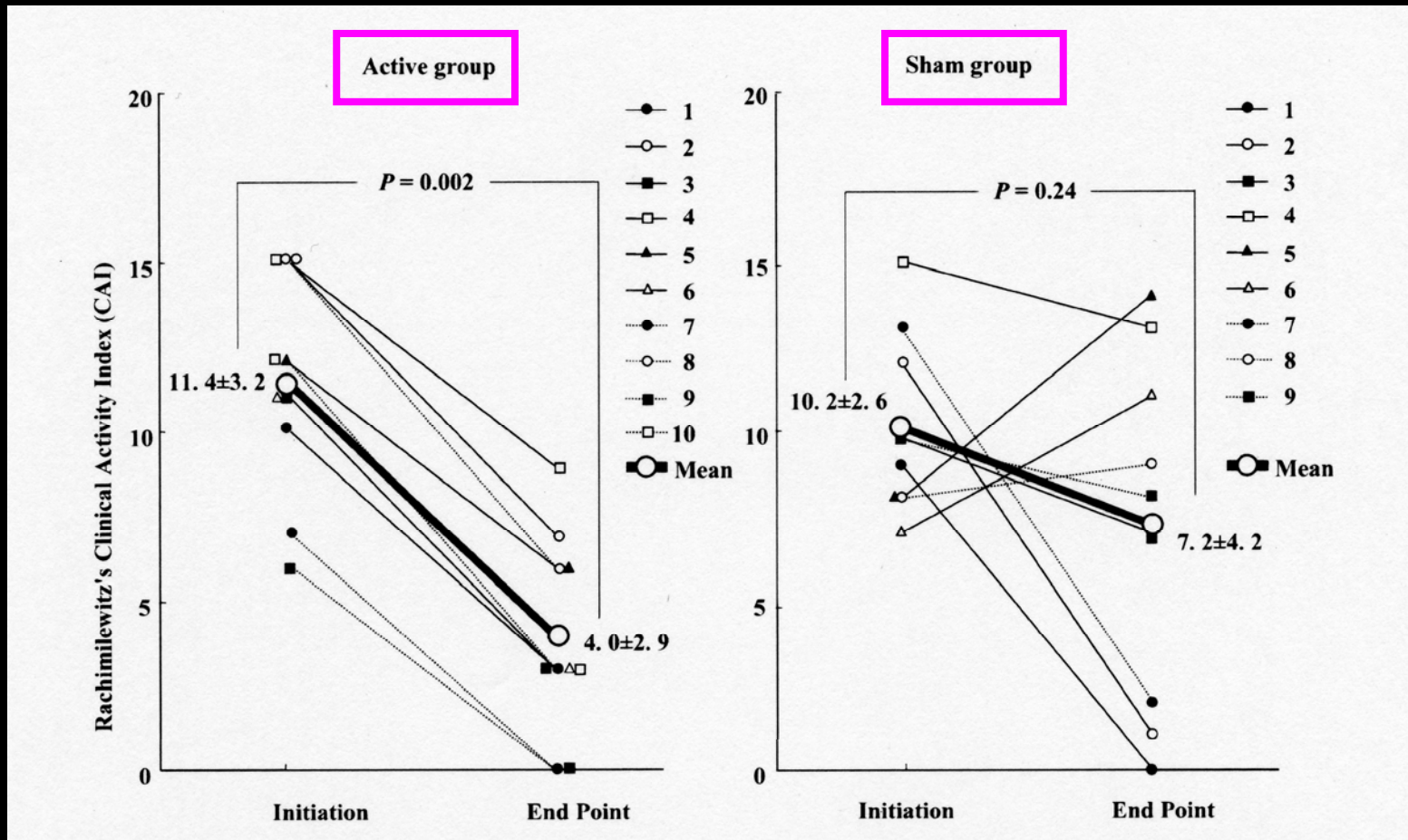
Steroid (prednisolone)

3.0 ~ 4.0 g/day of SASP or 1.5 ~ 2.0 g/day of 5-ASA

Cellsorba is more effective and safer than Prednisolone



A Multicenter, Double Blinded, Prospective Case-Control Study With Celsorba in Active UC



Cellsorba (n=10)

Sham (n=9)

Improvement Rate 80%, 8/10
(evaluated at week 10)

33%, 3/9

P < 0.05

Sawada K, Hibi T et al.; Am J Gastroenterol. 2005;100(6):1362-9.

Overview of the Pivotal Study of Adacolumn Therapy in US, EU and Japan for Moderate and Severe IBD

- **Randomized (2:1 scheme)**
- **Double-blinded, Placebo (sham)-controlled**
- **Multi-center (168 UC & 234 CD patients already enrolled in north America), EU and Japan participation**
- **Treat patients with moderate to severe UC or CD who failed or are intolerant to the standard therapies**
- **Patients are allowed to be on stable doses of 5-ASA, prednisone (up to 20 mg daily dose), 6-MP and azathioprine while in the study**
- **Patients will receive 10 treatments within 12 weeks**
- **Primary endpoint; clinical remission**

Pathophysiological Background-Based Treatment of IBD

