

# Targan & Bernstein IBD

- Triggers of flares
- C Difficile
- AZA/6MP
- Anti-TNF
- Pregnancy issues & IBD
- CyA/Inf in active UC
- Miscellaneous

# A Prospective Population Based Study of Triggers of Flares of IBD

CN Bernstein, S Singh, LA Graff, JR Walker, MS Cheang

- **Prospective**
- **Recruited from population-based research registry (UMIBDRR)**
- **completed mailed surveys q3 months for 1 yr (=5 surveys)**
- **Surveys assessed:**
  - Personal characteristics**
  - over past 3 months:*
    - Disease activity**
    - NSAID use**
    - Antibiotic use**
    - Infections**
    - Stressful life events and rating of impact**
    - Perceived stress (PSS)**
    - Positive / Negative affect (PANAS)**

# **Disease activity**

- **Manitoba IBD Index (MIBDI)  
(Am J Gastroenterol 2009)**

# **MIBDI**

**In the past 3 months my disease has been**

- (a) constantly active, giving me symptoms every day**
- (b) often active, giving me symptoms most days**
- (c) sometimes active, giving me symptoms on some days  
(for instance 1-2 days/week)**
- (d) occasionally active, giving me symptoms 1-2  
days/month**
- (e) rarely active, giving me symptoms on a few days in  
the past six months**
- (f) I was well in the past 6 months, what I consider a  
remission or absence of symptoms**

# Medications & Infections

- Medications: used in last 3 months?
  - **NSAIDs** – example types provided; frequency of use (daily to never)
  - **antibiotics** – if used, name and how long used
- **Infections:** in last 3 months?
  - Colds? check symptoms from list
  - Other infections; list type and approximate dates
  - Treatment

# Stress

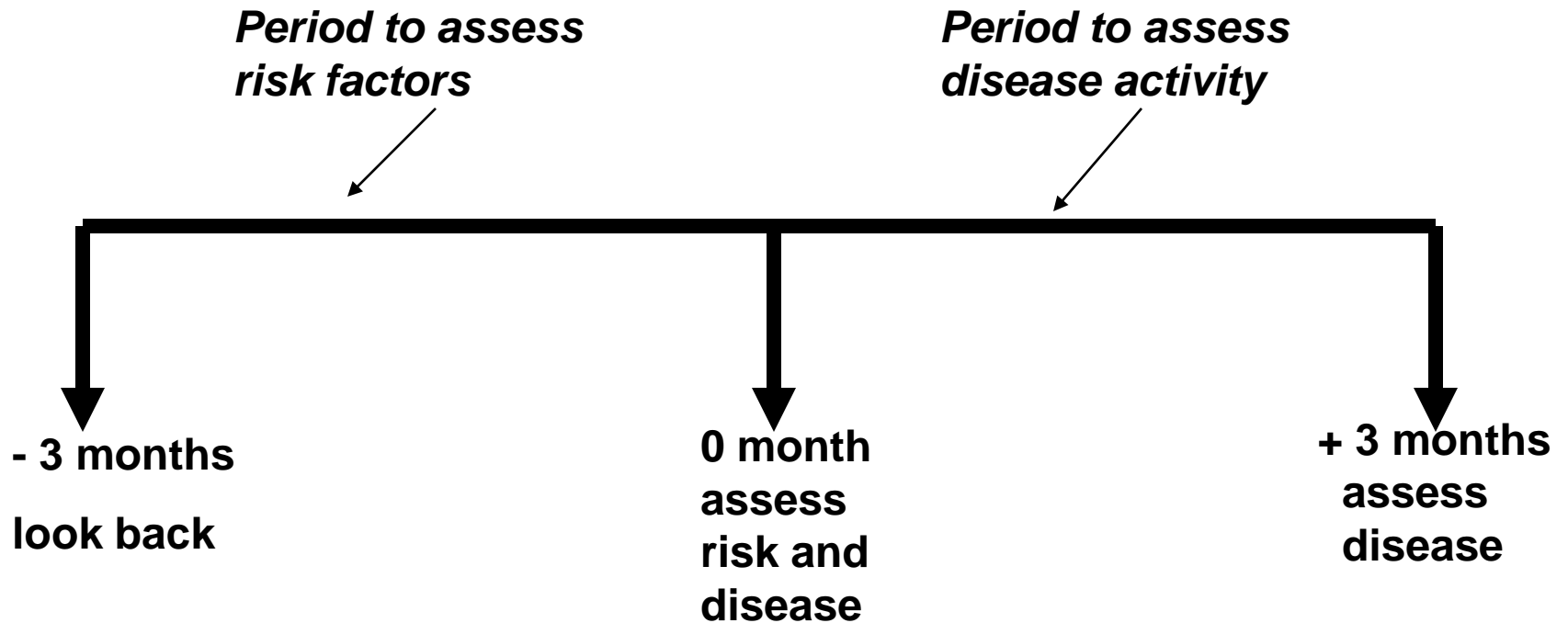
- **Life events**
  - List any major events in last 3 months
  - Rate each on stress level of 0-10
- **Perceived stress**
  - **Cohen Perceived Stress Scale** (Cohen et al J Health Soc Beh 1983)
  - assess degree to which situations in life are perceived as stressful
  - Stress levels over previous MONTH
  - 14 items; rating 1-5; overall score range=14-70
  - high vs low perceived stress by median split

# **PANAS** (Watson, Clark, Tellegen 1988)

- **20 items-past WEEK**
- **10 positive; 10 negative**
- **Rate items 1-5 (“very slightly to not at all”- “extremely”)**
- **Positive affect and negative affect differentially correlate with infection, symptoms of infectious diseases and chronic diseases**
- **High NA: subjective distress + unpleasurable engagement**
- **High PA: experiencing pleasurable engagement with the environment (enthusiasm, alertness)**
- **High NA relates to both depression and anxiety**
- **Low PA relates to depression and not anxiety**

# Assessment of risk factors

- Longitudinal assessment – repeated 5X



**Assess: Inactive / Inactive vs Inactive / Active**

# Results

- **Survey respondents:**

**Baseline (Q1): n=704**

**Q2: 602    Q3: 606    Q4: 601    Q5: 603**

- **Survey respondents with quarter of negative activity followed by quarter of positive activity n=174:**
- **Survey respondents with quarter of negative activity followed by quarter of negative activity n=209**

# Not associated with flare

	Inactive/Inactive	Inactive/Active
<b>Any use of NSAIDs</b>	<b>45.4%</b>	<b>49.7%</b> p=0.56
<b>Frequency of NSAID use</b>	<b>4.0</b>	<b>3.9</b> p=0.73
<b>Any infection</b>	<b>21.3%</b>	<b>21.1%</b> p=0.96
<b>Use of antibiotics</b>	<b>8.0%</b>	<b>9.6%</b> p=0.59
<b>Low positive affect</b>	<b>41.0%</b>	<b>49.4%</b> p=0.11

# Associated with flare

	Inactive/Inactive	Inactive/Active
<b>High perceived stress</b>	<b>29.2%</b>	<b>51.7%</b> p<0.0001
<b>High negative affect</b>	<b>30.7%</b>	<b>43%</b> p=0.015
<b>Any major stress event</b>	<b>43.5%</b>	<b>56.4%</b> p=0.013
<b>Major stress events total impact rating</b>	<b>5.0</b>	<b>7.2</b> p=0.004

# Correlation among affect and stress related variables

	Negative affect	Positive affect	Perceived stress	Major stress events total rating
Negative affect	<b>1.0</b>	<b>-0.42</b> <b>p&lt;0.0001</b>	<b>0.76</b> <b>p&lt;0.0001</b>	<b>0.4</b> <b>p&lt;0.0001</b>
Positive affect		<b>1.0</b>	<b>-0.53</b> <b>p&lt;0.0001</b>	<b>-0.13</b> <b>p=0.0024</b>
Perceived stress			<b>1.0</b>	<b>0.43</b> <b>p&lt;0.0001</b>
Major stress events total rating				<b>1.0</b>

# Multivariate analyses: Predictors of Flares

<b>High perceived stress (PSS)</b>	<b>2.46 (1.56-3.89)</b>
--	-------------------------

<b>Being single</b>	<b>1.79 (1.03-3.13)</b>
---------------------	-------------------------

# Conclusions

- **NSAID use, antibiotic use, recent infections are no more likely to be associated with flare of IBD than no flare**
- **Being single one is more likely to flare than if married**
- **Stressful life events are associated with a flare of IBD**
- **The greater the perception of stress the more likely to be associated with flare**

**C difficile**

- ***C. difficile*** is associated with IBD.
- Possible that IBD predisposes to acquiring ***C. difficile***.
- Increased prevalence of ***C difficile*** without Abs
- Ongoing use of Cipro- its assoc with ***C difficile***
- Is ***C difficile*** simply causing symptoms in its own right and not inducing a flare of IBD.

# **Rate of Recurrence of *Clostridium difficile* in Pediatric Patients with Inflammatory Bowel Disease**

JR Kelsen, DR Latta, T Zaoutis, KL McGowan, P Mamula, R Baldassano

**IBD n=138 control n= 80**

## **RISK FACTORS**

**IBD: 44% new onset IBD, 63% on immunosuppression, 33% on acid suppression prior to infection.**

**Prior antibiotic exposure: IBD=33% control=26% (p <0.2).**

**Prior hospitalization within 30 d: IBD= 10% control=27% (p< 0.002).**

## **OUTCOMES**

**The rate of recurrence of C Diff; IBD = 43% control= 7.5% (p <0.0001).**

**Effect on IBD disease severity:**

**-57% of IBD readmitted with an exacerbation of disease within 6 mo**

**-67% required escalation of therapy following CD infection.**

# **Opt-80 Versus Vancomycin in *Clostridium difficile* Infection: Results of a Randomized Clinical Trial**

M Miller, KM Mullane, K Weiss, A Lentnek, Y Golan, S Gorbach, P Sears, YK Shue, TJ Louie

- **Phase 3 macrocyclic bactericidal antibiotic**
- **+ve stool toxin test, 100 NA sites.**
- **PO OPT-80 (200 mg BID) vs PO vancomycin (125 mg QID) for 10 day**
- **Clinical cure (2 d post D/C Rx)**

**PP analysis: OPT-80=92%, vancomycin=90%**

**mITT: OPT-80=88%, vancomycin=86%**

- **Recurrence (4 wks post D/C Rx)**

**PP analysis: OPT-80 = 13%, vancomycin =24% p=0.005**

- **Global cure (clinical cure; no recurrence)**

**PP: OPT-80: 78%, vancomycin: 67%  $p=0.005$**

- **No diff in adverse events**

- **Better than Vanco; but still low global cure**

## **Phase II Efficacy of Human Monoclonal Antibody Treatment to Prevent *C. difficile* Recurrence**

I Lowy, B Leav, BM Blair, R Baxter, D Gerding, G Nichol, R Kohberger, M Leney, S Sloan, DC Molrine, DM Ambrosino

- **Metro or Vanc single IV infusion of 10mg/kg CDA1 +10mg/kg of CDB1 vs NS**
- **Efficacy and safety outcomes were assessed for 84 days after infusion**
- **Recurrence of CDI = new episode of diarrhea +ve stool toxin test following resolution of prior CDI + D/C Abs**
- **N=200 from 30 sites;**
- **Infection with BI/NAP1/027 strain (32.5% vs. 25.7%, p=0.38),**
- **History of prior CDI (28.7% vs. 32.7%, p=0.64)**
- **Inpatient status at enrollment (49.5% vs. 52.5% p=0.67).**

## **RESULTS**

- **ITT Recurrence Rate (6.9% vs. 25.3%, p=0.0004).**
- **Epidemic BI strain (RR 8.0% vs. 31.6% p=0.06)**
- **Prior hx of CDI (RR 6.9% vs. 37.5 %, p=0.006).**
- **SAE higher in the placebo arm, including dehydration (0% vs. 5%, p=0.03) and hypotension (0% vs. 7%, p=0.01).**
- **Subjects hospitalized after infusion during the 84 day study period was reduced in the CDA1+CDB1 arm (8.91% vs. 20.2%, p=0.028).**

# **Anti-TNF Rx**

**One Year Data from the SONIC Study:  
A Randomized, Double-Blind Trial Comparing Infliximab and  
Infliximab plus Azathioprine to Azathioprine in Patients with  
Crohn's Disease Naive to Immunomodulators and Biologics**

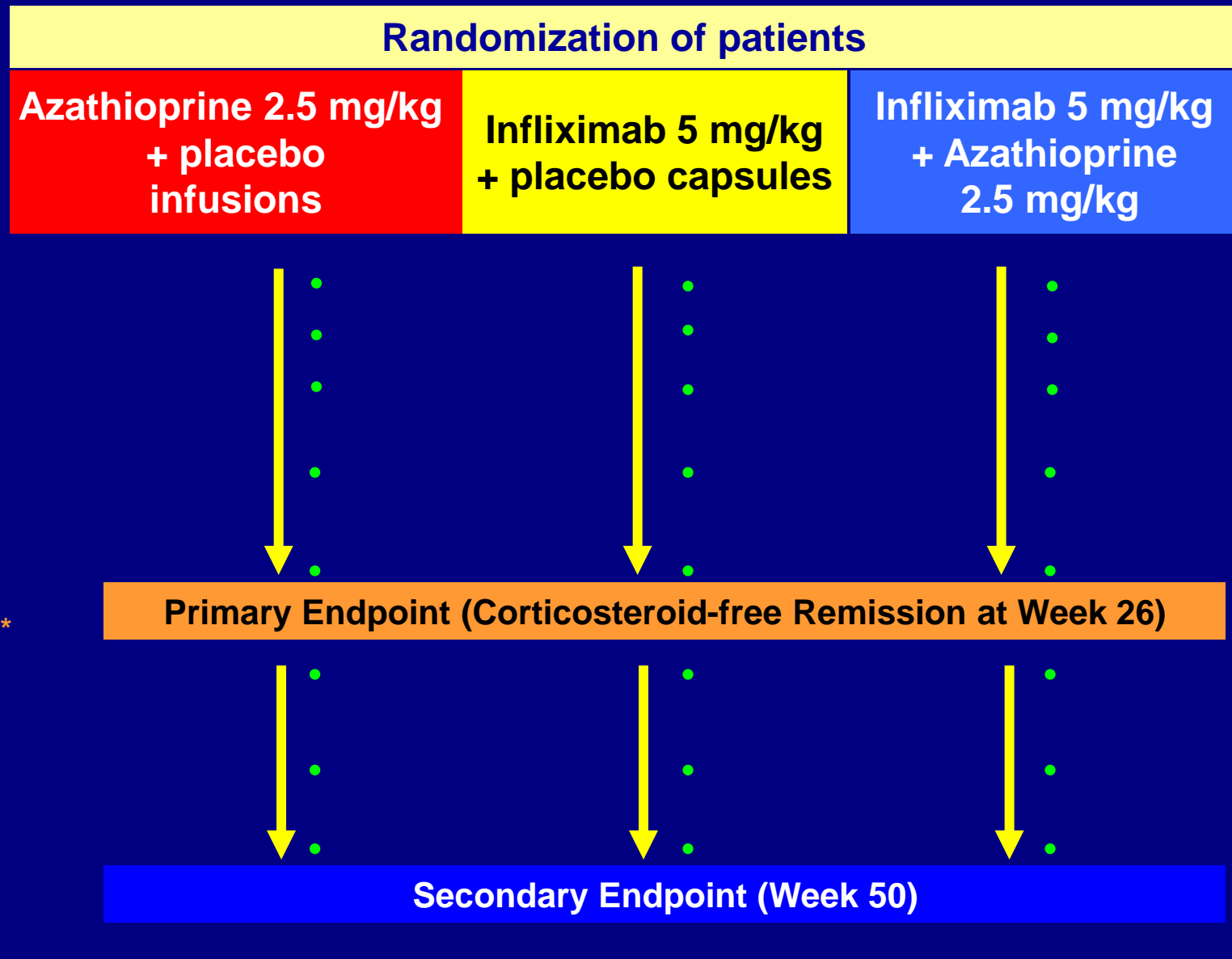
W Sandborn, P Rutgeerts, W Reinisch, G Mantzaris, A Kornbluth D  
Rachmilewitz, S Lichtiger, G D'Haens, C Janneke van der Woude,  
R Diamond, D Broussard, R Hegedus; JF Colombel

# **One Year Data from the SONIC Study: A Randomized, Double-Blind Trial Comparing Infliximab and Infliximab plus Azathioprine to Azathioprine in Patients with Crohn's Disease Naive to Immunomodulators and Biologic Therapy**

---

**William Sandborn, MD; Paul Rutgeerts, MD;  
Walter Reinisch, MD; Gerassimos Mantzaris, MD;  
Asher Kornbluth, MD; Daniel Rachmilewitz, MD;  
Simon Lichtiger, MD; Geert D'Haens, MD;  
C Janneke van der Woude, MD;  
Robert Diamond, MD; Delma Broussard, MD;  
Ronald Hegedus; Jean Frederic Colombel, MD**

# SONIC Study Design



Main

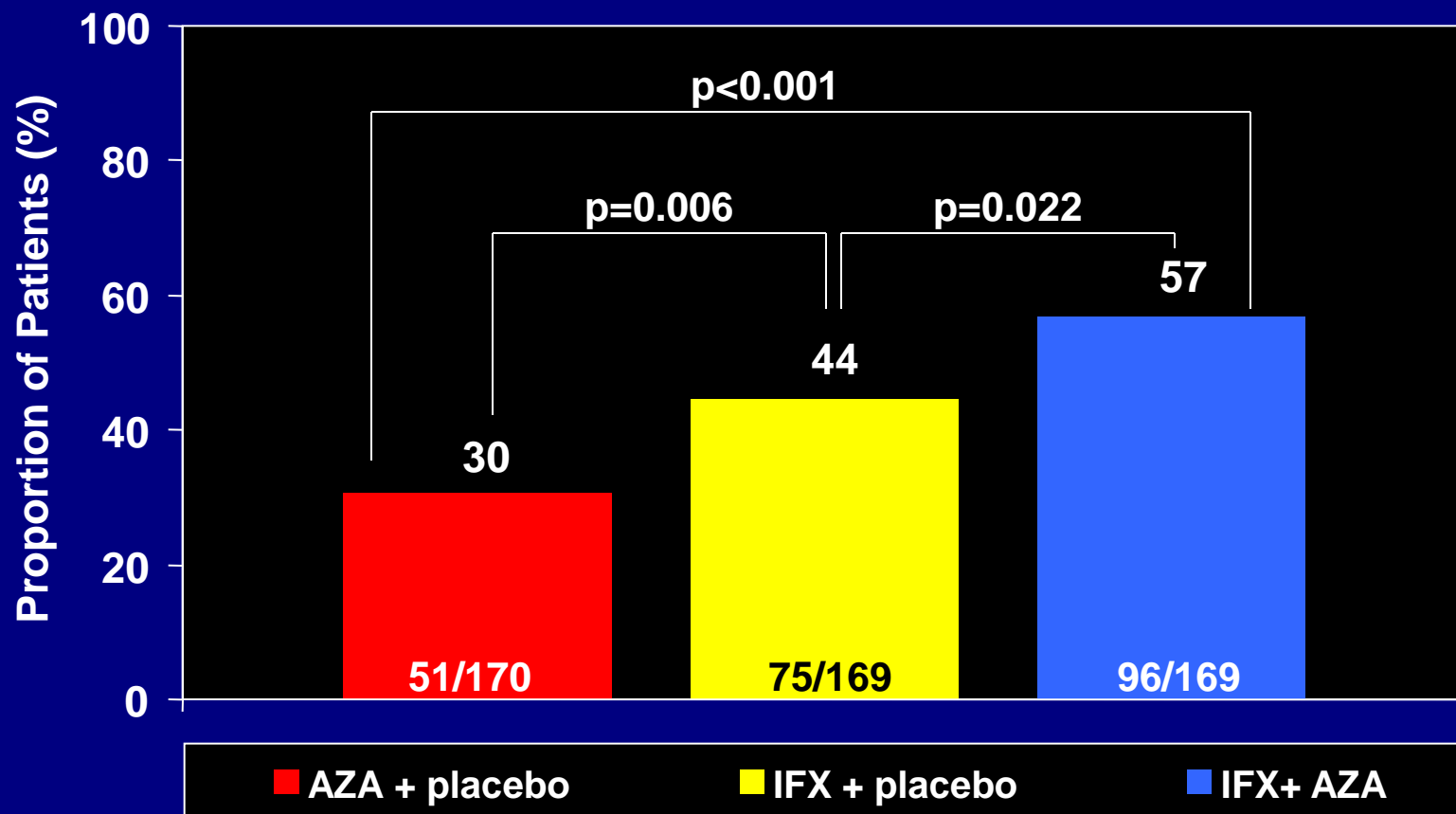
Extension

• Infusions

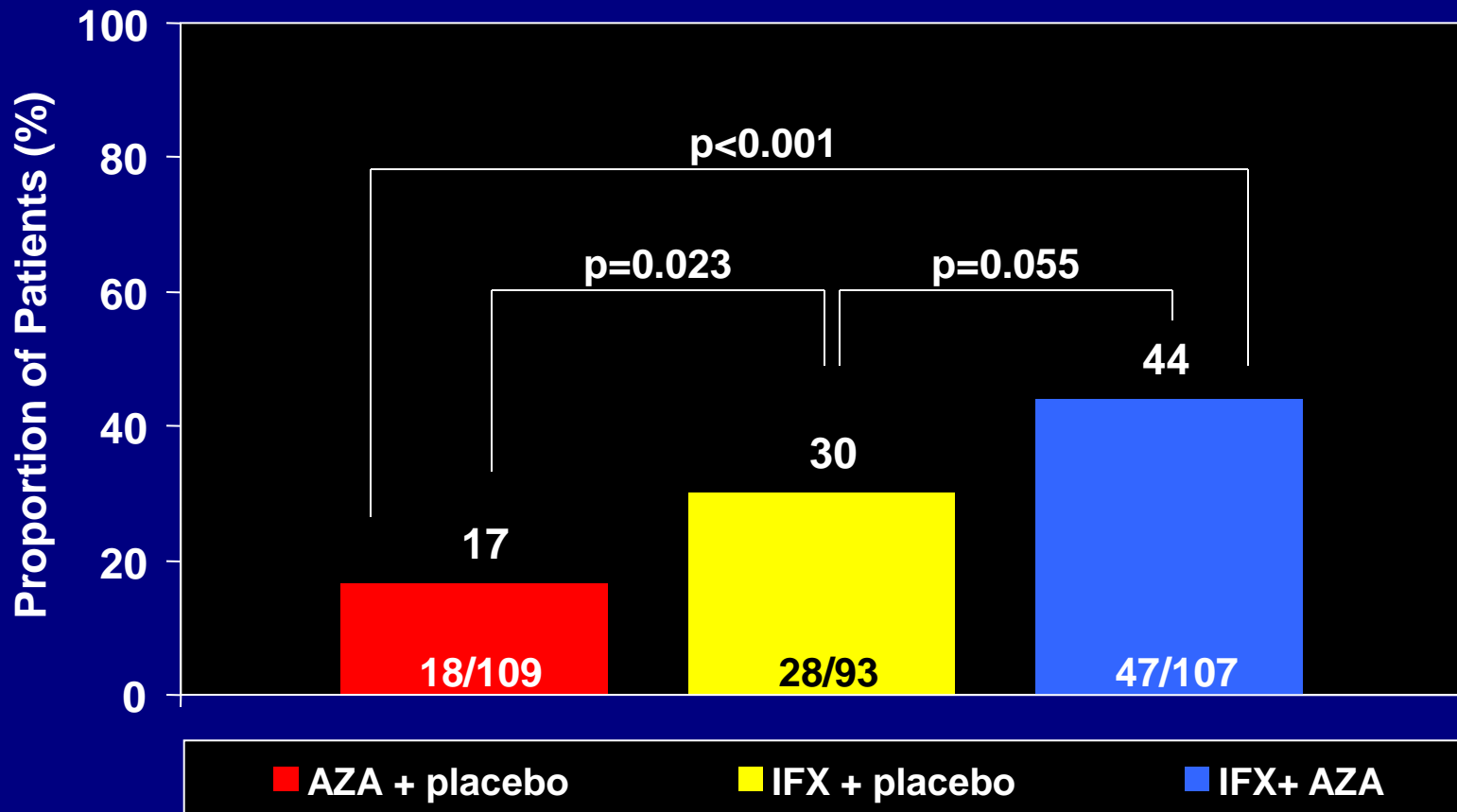
\* Endoscopy performed at Weeks 0 & 26

# Clinical Remission Without Corticosteroids at Week 26

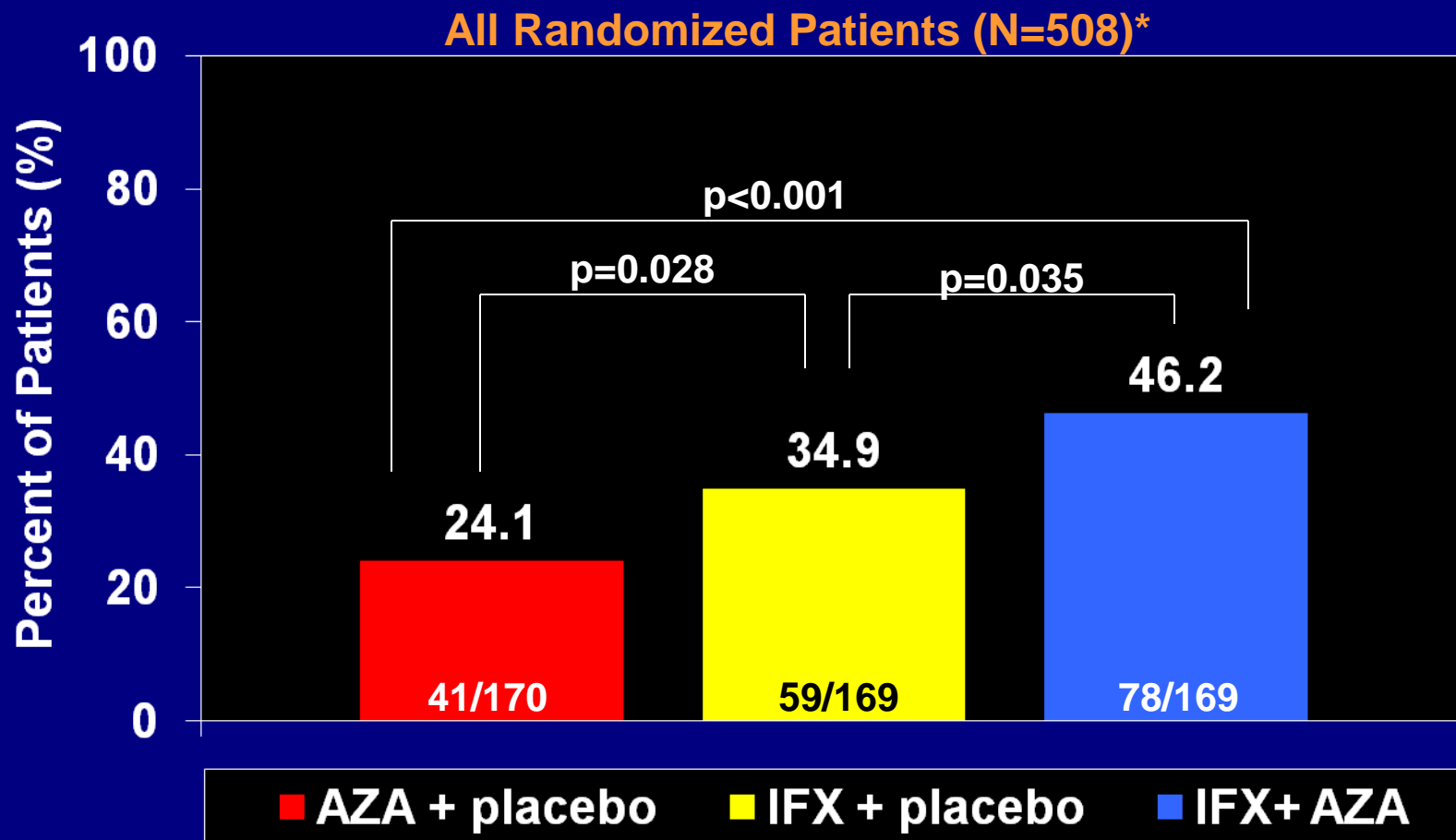
## Primary Endpoint



# Complete Mucosal Healing at Week 26

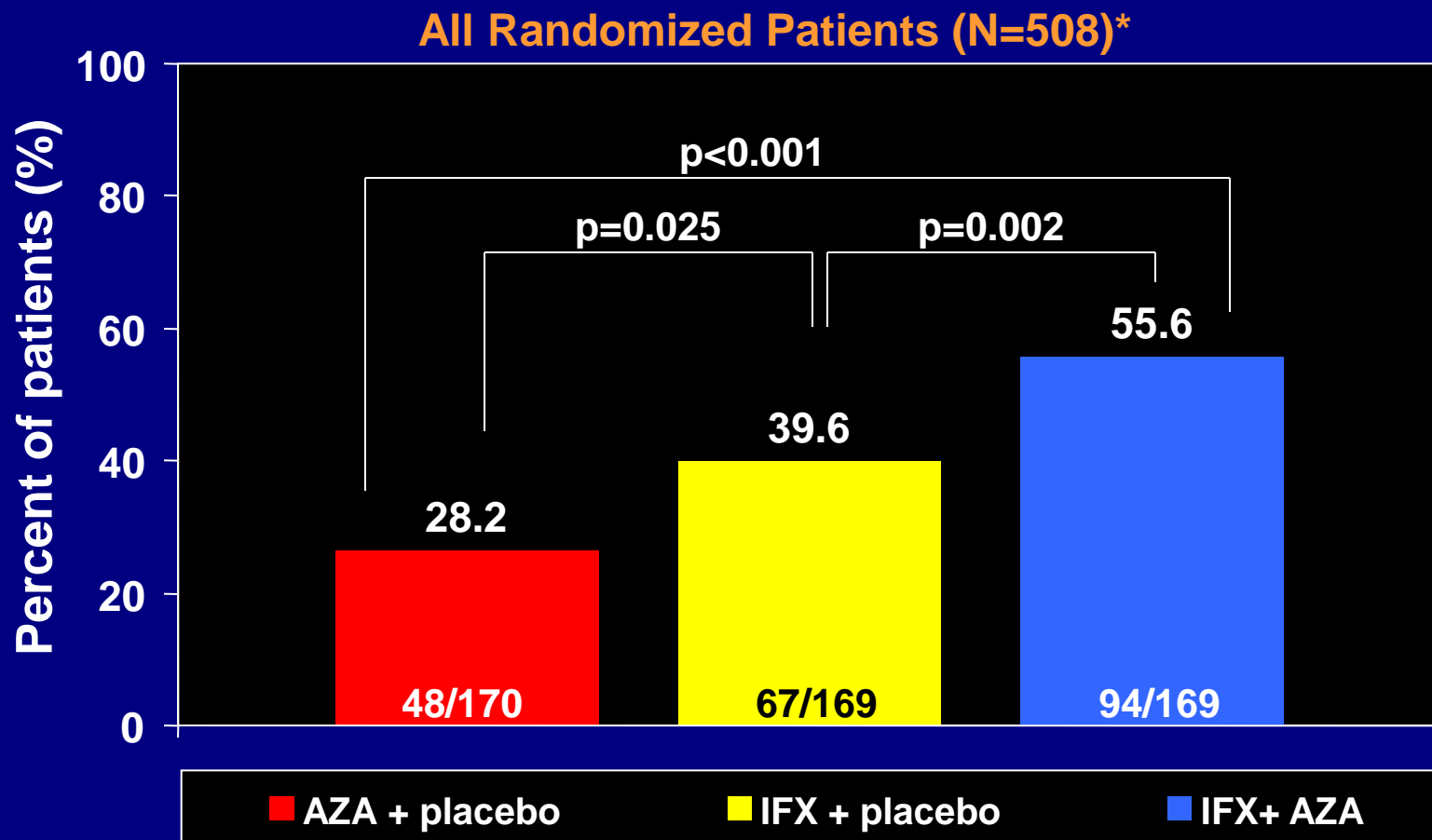


# Corticosteroid-Free Clinical Remission at Week 50



\* Patients who did not enter the Study Extension were treated as non-responders

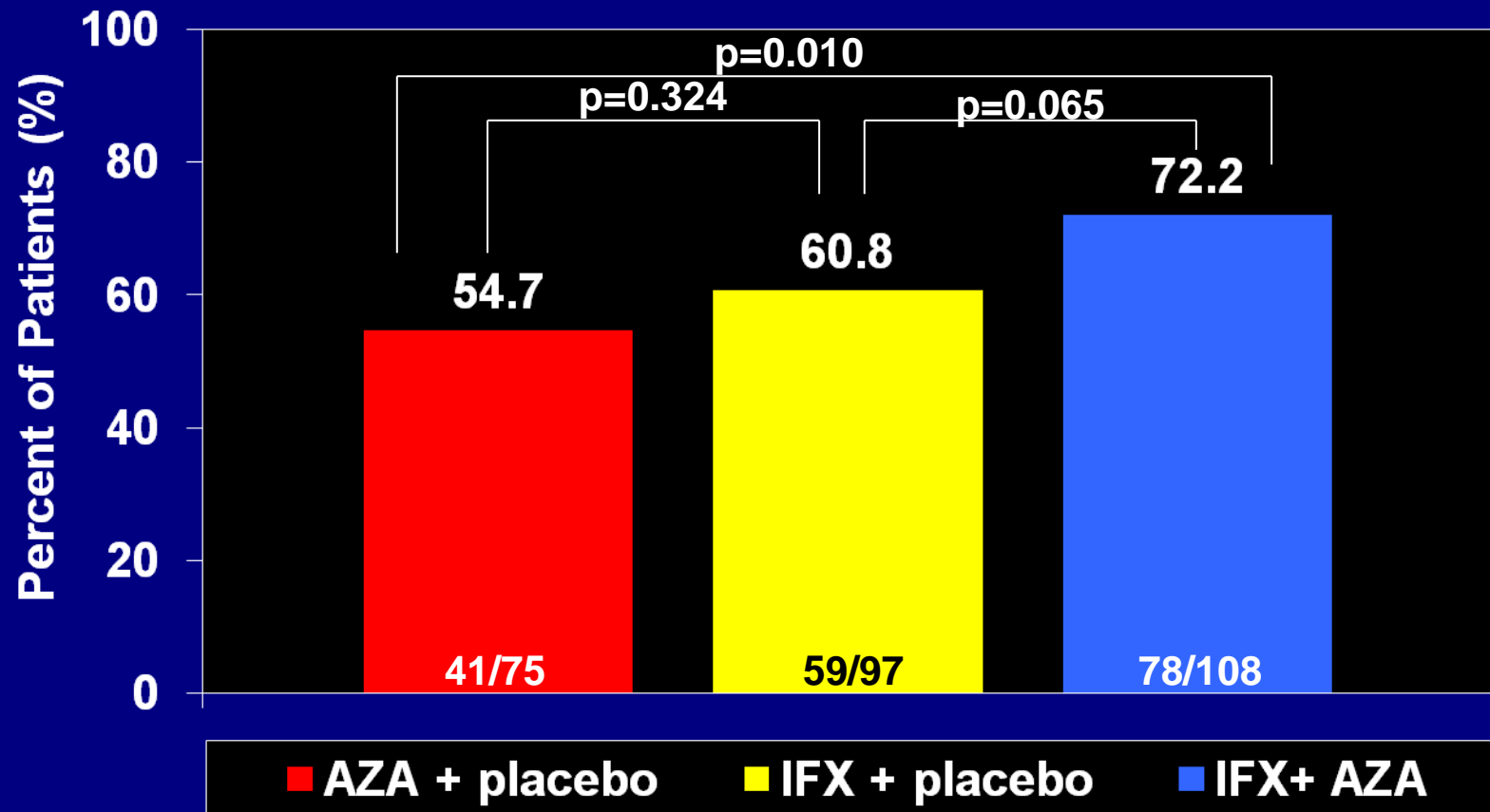
# Corticosteroid-Free Clinical Remission at Week 50



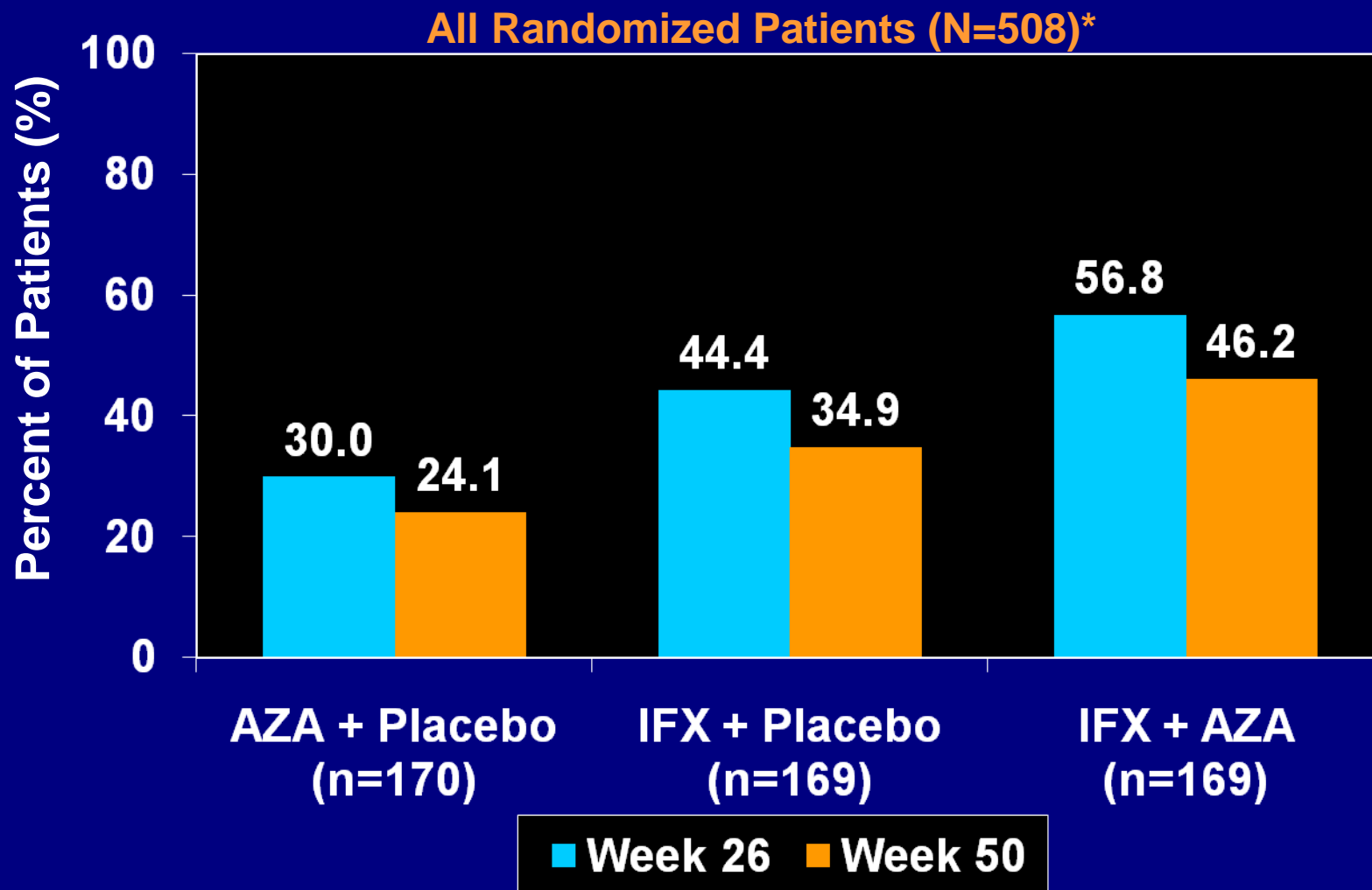
\* Patients who did not enter the Study Extension had **Week 26 values carried forward**

# SONIC Corticosteroid-Free Clinical Remission at Week 50

Patients Enrolled in the Extension (N=280)



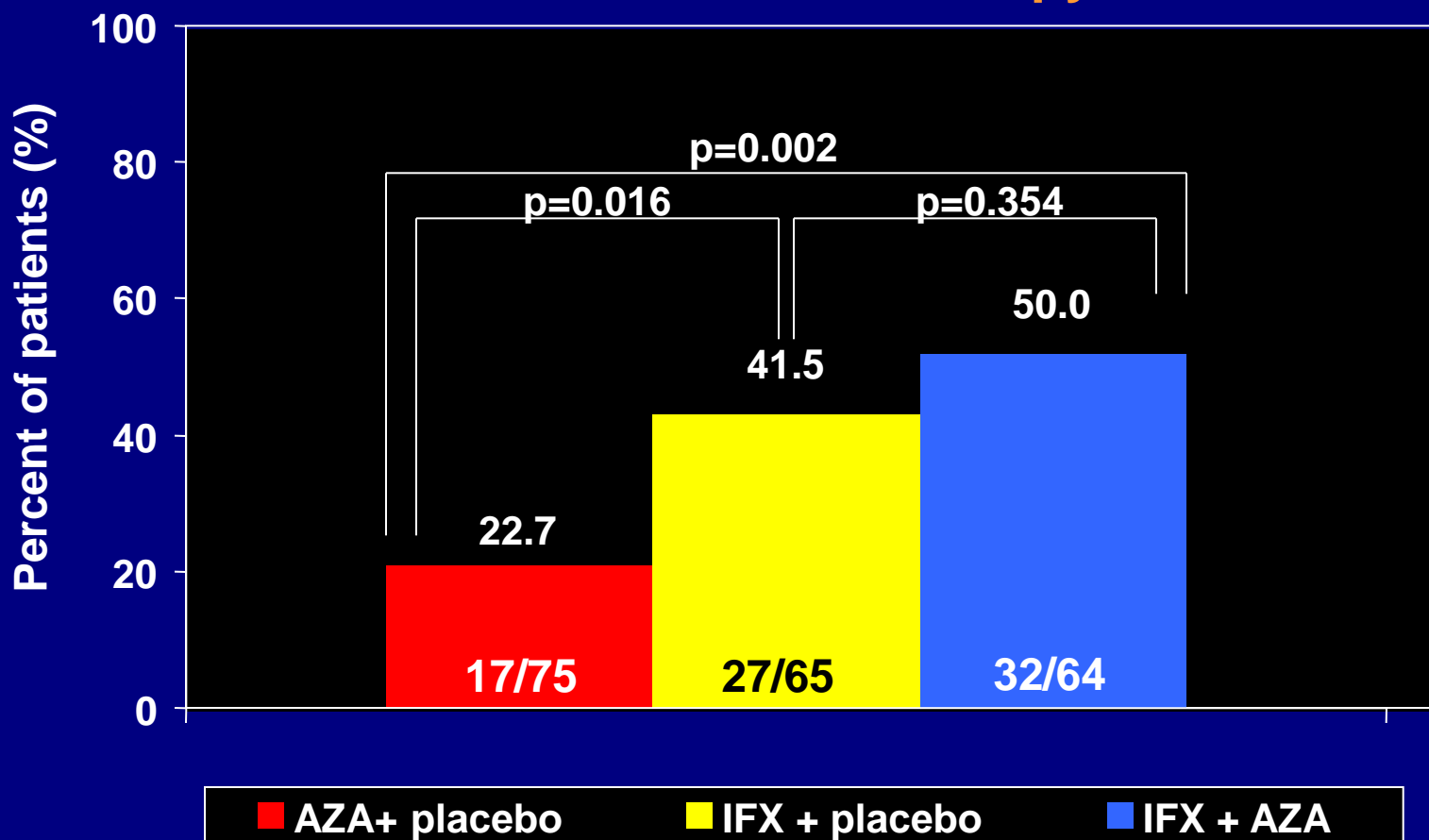
# Patients in Corticosteroid-Free Clinical Remission at Weeks 26 & 50



\* Patients who did not enter the Study Extension were treated as non-responders

# Corticosteroid-Free Clinical Remission at Week 50

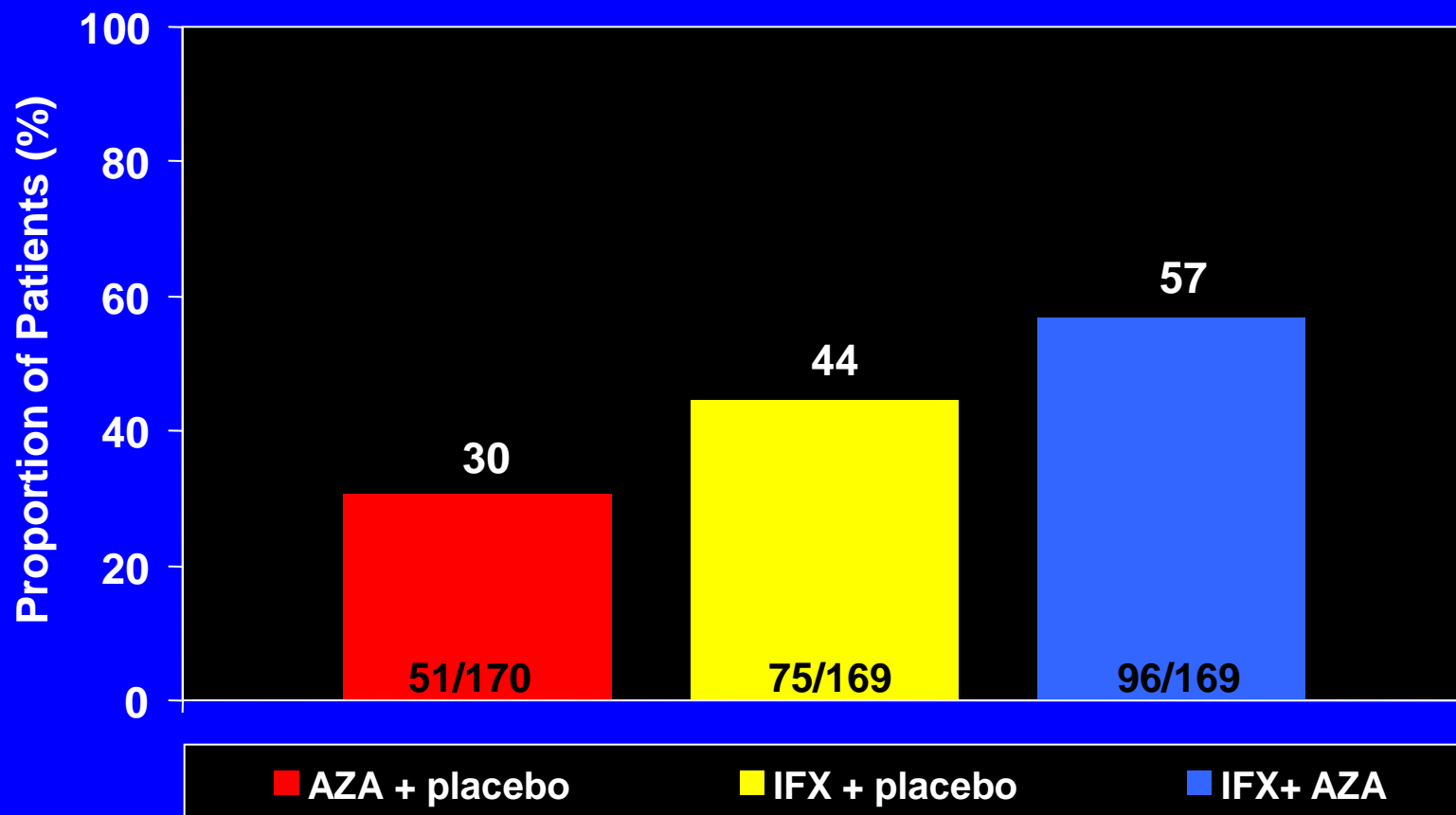
Patients with CRP  $\geq 0.8$  mg/dL and Lesions on Baseline Endoscopy\*



\* Patients who did not enter the Study Extension were treated as non-responders

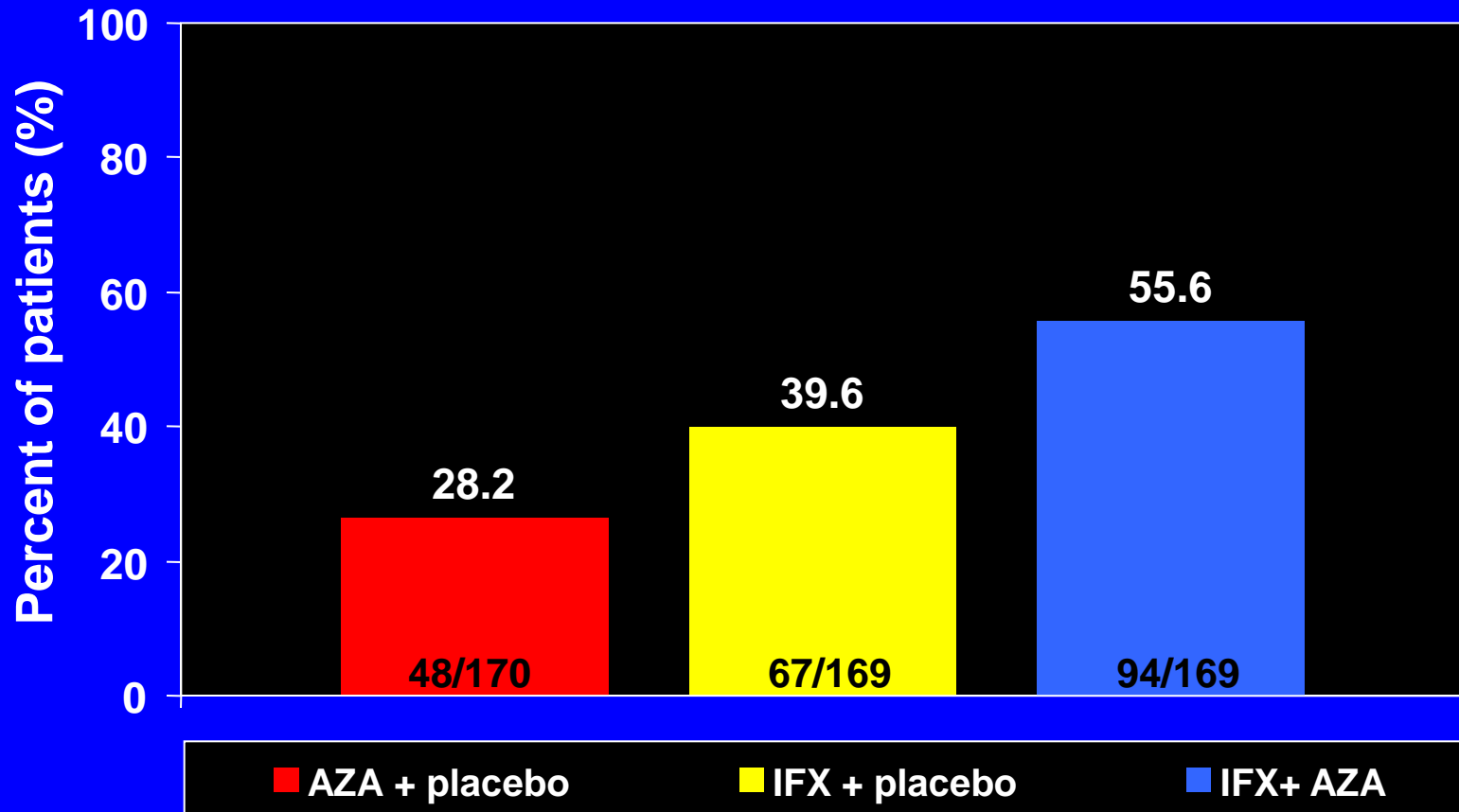
# Without Corticosteroids at Wk 26

## Primary Endpoint



# Corticosteroid-Free Clinical Remission at Week 50

All Randomized Patients (N=508)\*



\* Patients who did not enter the Study Extension had Week 26 values carried forward

# **Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission On Combined Therapy with Immunosuppressors: A Prospective Ongoing Cohort Study**

**E Louis, G Vernier-Massouille, JC Grimaud, Y Bouhnik, D Laharie, JL Dupas, H Pillant, L Picon, M Veyrac, M Flamant, G Savoye, R Jian, M De Vos, G Paintaud, E Piver, JF Colombel, JY Mary, M Lemann**

- **Luminal CD patients Rx >1 y with IFX + IS and in stable remission without steroids for > 6 mos were prospectively recruited.**
- **n=115 Med duration of IFX (2.2 y) + IS (2.8 y).**
- **After a med f/u 12 mos, 45 relapses have been observed.**
- **Multivariate analysis, a model based on:**
  - CDEIS ( $\geq 2$ , HR=3.0, P<0.001)**
  - CRP ( $\geq 5$  mg/l, HR= 3.8, P<0.001)**
  - Hg ( $\leq 14.5$ g/dl, HR=4.7, P=0.002)**
  - IFX trough levels ( $\geq 2$ microg/ml, HR=2.9, P=0.006)**

- **37 relapsers are currently evaluable 4 weeks**
- **After IFX re-infusion for response to IFX retreatment: 36/37 were in remission and none experienced acute or delayed reaction.**

# Conclusion

**After stable remission with IFX + IS Rx for >1 y, >50% of patients have not relapsed at 1 y after D/C IFX.**

**In relapsers, IFX re-treatment was well tolerated and induced remission in the short term. A subgroup of patients with very low risk of relapse could be identified through a combination of biological and endoscopic markers.**

- **Psoriasis and anti-TNF**

# BSR-register of anti-TNF/RA

9826 pts followed mean of 2.64yrs.

25 incident cases of Psoriasis.

Etanercept was used in 40%      0.59/1000 pt yrs

Infliximab used in 33%      0.88/1000 pt yrs

Adalimumab used in 28%      1.84/1000 pt yrs

13 pts in first 6mos, rest between 12-24 mos.

2 after D/C @ 4 and 6 months.

8 pts D/C drug (6 improved)

# Pathogenic issues-psoriasis

Innate immunity-pre-dendritic cells +virus→ IFNalpha

PDC +IFNalpha→active Dendritic cells

Adaptive immunity: IFN +T cells→ Th1 responses

**Psoriatic lesions contain active IFN alpha**

**IFN regulatory factor(IRF)-/- mice→psoriasis**

**Rx of psoriatic pts with IFN alpha *can* aggravate psoriasis**

# ? Discordance in Targeted Therapies

- **Targeting specific T-cell costimulatory molecules with biologic response modifiers such as alefacept (fusion protein of IgG1 and LFA-3 is effective for psoriasis but not as effective for PsA**
  - » Mease PJ, Arthritis Rheum May 2006
- **Efalizumab a humanized monoclonal antibody against LFA-1 is effective in psoriasis**
  - may exacerbate or trigger the onset of PsA
    - Papp KA, J Cutan Med Surg. Mar 2007
- **Blockade of IL-12/23 results in dramatic response in psoriasis**
  - ??? response in PsA appears to be less dramatic
    - » Gottlieb A, Lancet, February 2009

# **Psoriasis and Eczema Skin Lesions Associated with TNF-Blockade Therapy in IBD: Natural History and Clinical Characteristics**

Jf Rahier, S Buche, L Peyrin Biroulet, M Lémann, M Allez, J Cosnes, Y Bouhnik, E Delaporte, JF Colombel

- **41 patients (35 CD, 5 UC; 34 women, 7 men; mean age 27 years)**
- **psoriasis n=27, eczema like n=14.**
- **16/27 (65%) had a personal or familial history of skin diseases that was an inflammatory skin disease.**
- **Psoriasis lesions: tinea amiantacea and flexural psoriasis**
- **Eczema like lesions had variable localization**
- **Skin lesions emerged while IBD was quiescent in 31**
- **32 infliximab, 6 adalimumab and 3 certolizumab**

- **All patients were treated with topical corticosteroids and keratolytics**
- **Partial or total remission n= 28, stable skin disease n=7, No f/u, n=6.**
- **Psoriasis: switching anti-TNF once or twice associated with recurrence (16/16)**
- **Switching less frequent for eczema-like lesions, recurrence rate was (2/5).**
- **Definitive cessation of anti-TNF due to skin was necessary in n=7.**

- **inflammatory skin lesions induced by anti TNF inhibitors were characterized by**
- **(1) strong association with female gender,**
- **(2) high frequency of personal or familial history of skin disease,**
- **(3) absence of correlation with intestinal disease activity,**
- **(4) lack of improvement of psoriasis lesions after switching the anti-TNF**
- **(5) need for anti-TNF cessation in 17% of patients.**

# **Infliximab-Induced Psoriasis in Pediatric Crohn Disease; Experience of This Paradoxical Skin Manifestation At a Tertiary Centre and a Potential Association with a Variation in the IL-23r Gene**

ME Sherlock, TD Walters, M Zachos, A Muise, AM. Griffiths

- **118 children received Inf from 01/00 to 08/08.**
- **13 children (11%), (9 males), developed new onset psoriasis following Inf Rx.**
- **Median duration of Inf exposure at the time of psoriasis onset was 1.0 yr (IQR 0.6 - 2.1).**
- **11/13 responded well to topical steroid therapy. 2 patients discontinued Inf, both with resolution of their psoriasis.**

**DNA available on 8 /13 who developed psoriasis,**

- 137 disease-matched controls & 86 UC.**
- 75% of cases were homozygous for the II-23R rs10489629 SNP polymorphism v 42% of CD controls and 28% of UC**
- OR for an infliximab-exposed patient developing psoriasis was 3.8 for heterozygotes and 14 for homozygotes (p=0.07).**

**AZA/6-MP**

# **Mercaptopurine Rescue After Azathioprine-Induced Liver Injury in Inflammatory Bowel Disease**

F Bermejo, A López-San Román, A Algaba, M Van Domselaar, JP Gisbert, JA Carneros, E Garrido, P Valer, M Rodríguez-Gandía, B Piqueras

- **14 CD, 16 UC, on AZA therapy with liver injury**
- **Mean age was  $50\pm 15$  ys; 63% were male**
- **Mean AZA dose was  $2.2\pm 0.4$  mg/kg/d.**
- **Mean time of AZA exposure when liver injury was first detected was 3 months (range 0.5-11 mo).**
- **Type of liver injury:**
  - hepatotoxic 33%, mean ALT = 175 U/mL (nl < 40)
  - cholestatic 40%, mean alk phos=194 U/L (nl < 135).
  - mixed 27%.

- **After a mean of 2.5 months (range 0-11), Rx was switched to 6-MP at a mean dose of  $1.3 \pm 0.3$  mg/kg/d.**
- **In 87% of cases, 6-MP was tolerated with normalization of liver tests and without further liver injury; of these, 77% tolerated full 6-MP doses, and 10% tolerated lower doses.**
- **In a further 13%, liver injury reappeared (2= cholestasis & 1=mixed injury), 1-3 mo after the onset of 6-MP exposure**

# **Split-Dose Administration of 6-MP/Aza: Effective Novel Strategy for IBD Patients with Preferential 6MMP Metabolism**

DQ Shih, M Nguyen, P Ibañez, LY Kwan, SR Targan, EA Vasilias

- **Splitting the daily dose of thiopurine can reduce 6MMP while maintaining 6TGN levels and clinical efficacy.**
- **Retrospective chart review of 100 IBD patients treated at CSMC with AZA or 6MP**
- **Preferential metabolizers with baseline 6MMP levels > 7000 pmol/8×10<sup>8</sup> RBC who underwent split dosing were identified and assessed**
- **12/100 were preferential metabolisers to 6MMP underwent split-dosing of AZA or 6MP without other concomitant intervention.**

- **Result: significant reduction in 6MMP levels (11119 vs. 5326 pmol/8×10<sup>8</sup> RBC; p=0.0001) without adversely affecting clinical disease activity or 6TGN levels (239 vs. 229 pmol/8×10<sup>8</sup>).**
- **6-MMP associated side effects (increased LFT, leukopenia, and flu-like sx) improved in all patients.**
- **After mean f/u 40 mos, Rx biologics (n=4), surgery (n=1), and remain on split dose of AZA or 6-MP with control of their IBD (n=7).**

**CyA-----Inf**

**Inf-----CyA**

**Active UC**

# Successive Treatment with Cyclosporine and Infliximab in Severe Ulcerative Colitis (UC)

S Leblanc, M Allez, P Seksik, B Flourie, H Peeters, JL Dupas, G Bouguen, L Peyrin Biroulet, A Bourreille, O Dewit, Y Bouhnik, PF Michetti, S Chaussade, P de Saussure, JF Colombel, M Lemann

- 65 CyA first-Inf given within 2d (0-31)

of CyA withdrawal

- 21 Inf first-CyA given within 17 days (0-58) of Inf infusion.
- Steroids given in 86%
- Immunosuppressants (AZA or MTX) in 73%
- Probability of avoiding colectomy was 61% at 3 mo, 41% at 1 yr and 37% at 3 yr (K-M)
- 1 death-post op PE; otherwise usual SAE

# Sequential Ciclosporine and Infliximab Rescue Therapy in Steroid Refractory Ulcerative Colitis

AM O'Toole, D Keegan, H Mulcahy, DP O'Donoghue

- 22 CyA first, 8 ADA/Inf first
- 23 pancolitis
- Med time between Rx was 1.1 mos (1 d to 8 y)
- 20 failed-colectomy
- 10 succeeded-4 AZA, 5 anti TNF @ med 315 d

# **Pregnancy & IBD**

# Pregnancy Outcomes: Population Based Studies

	IBD	UC	CD
Preterm Birth	X	X	X X
LBW	X		X XX
SGA			X
Congenital Malformation		XX	
Caesarean Section	XX		

1. Kornfeld: Am J Obstet Gynecol 1997 (n=756 IBD)
2. Fonager: Am J Gastroenterol 1998 (n=510 CD)
3. Norgard: Am J Gastroenterol 2000 (n=1531 UC)
4. Dominitz: Am J Gastroenterol 2002 (n=107 UC, 155 CD)
5. Mahadevan: Gastroenterology 2007 (n=300 UC, 154 CD)

# **The Effect of Inflammatory Bowel Disease (IBD) During Pregnancy On Long-Term Health and Illness in Children of IBD Patients-a Multicenter Israeli Study**

I Dotan, A Alper, D Rachmilewitz, S Odes, I Chermesh, G Fraser, V Peles, S Reif

- **146 IBD mothers (93 CD, 53 UC), 70 controls (C).**
- **IBD mothers --385 children (age  $16 \pm 10.8$  yrs, 52.8% born after IBD diagnosis) C--144 children (age  $13 \pm 9$  years).**
- **75% using either no Rx or 5-ASA (8% AZA, 0 antiTNF)**
- **Mean mother age:  $43 + 10$  vs.  $39 + 8.3$  years in IBD vs. controls.**
- **Disease duration:  $10.8 \pm 7.5$  years.**
- **IBD exacerbation (33%), mostly (45%) during the T1**

**IBD patients had more**

- **SA IBD:  $0.68 \pm 1.2$  C :  $0.33 \pm 0.6$  in controls,  $p=0.01$ .**
- **LBW IBD:  $3.13 \pm 0.6$  C:  $3.27 \pm 0.45$  kg,  $p=0.005$ .**

***“Doctor, will my IBD have an effect on my child?”***

# ***IBD in pregnancy has a long-term effect on offspring's morbidity***

	IBD (%)	Control (%)	P
IBD	2.8	0	0.045
Wheezing bronchitis	9	18	<0.05
Atopic dermatitis	5.5	11.1	0.028
ADHD	5	0.8	0.03
Gross motor abnormalities	4.4	0.7	0.04
>3 Intercurrent infections	23, 20, 17 1st, 2nd, 3rd y	42, 46, 53 1st, 2nd, 3rd y	0.001

More methylphenidate (ritalin) use in CD (5.4%) vs. UC (0%) offspring (p=0.02)

- Adolescent height IBD :  $1.28 \pm 0.41$  C:  $1.47 \pm 0.33$ m,  $p < 0.01$
- Adolescent weight IBD :  $29.3 \pm 21$  C:  $39 \pm 24$  kg,  $p < 0.01$

***Conclusion:***

***IBD, before and after diagnosis, has significant and diverse short and long-term effects on the health and Development of IBD mothers' offspring:***

***abortions, birth weight, teenage weight and height, concomitant diseases and neurologic abnormalities***

# **Fertility and Outcomes of Pregnancies Fathered By Male Patients Exposed to Thiopurines**

C Teruel, A López-San Román, C Taxonera, A Algaba, JP Gisbert, JL Perez-Calle, M Martín-Arranz, M Van Domselaar, J Estellés, F Bermejo, PM Linares, P Lopez-Serrano

- **Any exposure to thiopurines during the 3 months preceding conception**
- **44 pregnancies in thiopurine gp**
- **74 pregnancies in no thiopurine within 3 mo**
- **No differences regarding negative pregnancy outcomes (preterm delivery, abortion, LBW, malformations)**

# **Pregnancy Outcome in Inflammatory Bowel Disease for Women Treated with Thiopurine: Cohort from the CESAME Study**

J Coelho, L Beaugerie, JF Colombel, X Hebuterne, E Lerebours, M Lemann, P Baumer, J Cosnes, A Bourreille, JP Gendre, P Seksik, F Carrat, P Marteau

- **138 births/215 pregnancies in 204 women in the CESAME cohort 05/04 to 10/07**
- **median age=28.4 y,**
- **mean disease duration=6.8 y**
- **CD=76% UC= 22, IBDU=2.5**

	<b>Thiopurines</b>	<b>Other Rx</b>	<b>None</b>
<b>Pregnancies</b>	<b>40%</b>	<b>39%</b>	<b>21%</b>
<b>Terminated</b>	<b>36%</b>	<b>33%</b>	<b>40%</b>
<b>Prematurity</b>	<b>22%</b>	<b>16%</b>	<b>15%</b>
<b>Cong Ab</b>	<b>3.6%</b>	<b>5.3%</b>	<b>3.7%</b>
<b>LBW</b>	<b>14.5%</b>	<b>12.5%</b>	<b>7.4%</b>

**AZA/6MP not associated with increased pregnancy risk**

# **Pregnancy Outcomes in Women Exposed to Adalimumab: the OTIS Autoimmune Diseases in Pregnancy Project**

**DL Johnson, KL Jones, CD Chambers, E Salas**

- **Prospective cohort**
- **RA on ADA in T1 (44% D/C in T1, 38% thru T3),**
- **RA on another RX,**
- **healthy (no RA or ADA)**

## **MAJOR STRUCTURAL DEFECTS**

- **RA/ADA: 2/34 (5.9%)**  
**(1 undescended teste and 1 microcephaly).**
- **RA/other: 2/53 (3.8%)**  
**(1 chromosomal abn; 1 club feet).**
- **Healthy: 2/47 (4.3%).**

- **Case series; ADA in other diseases (n=109):**
- **9 (8.3%) major anomalies had been reported**
- **3 chromosomal anomalies,**
- **1 spina bifida with hydrocephalus,**
- **1 bicuspid aortic valve and agenesis of the corpus callosum,**
- **1 VSD,**
- **1 congenital hip dysplasia with inguinal hernia,**
- **1 non-specific heart anomaly**
- **1 congenital hypothyroidism.**

# CONCLUSION (authors')

- **Based on these preliminary data, no concerns have been raised regarding increased risks for adverse pregnancy outcomes associated with early pregnancy exposure to ADA in the treatment of RA. Firm conclusions await accumulation of sufficient sample size in this prospective**

**A Multi-Center National Prospective Study of Pregnancy and Neonatal Outcomes in Women with Inflammatory Bowel Disease Exposed to Immunomodulators and Biologic Therapy**

U Mahadevan, CF Martin, RS Sandler, SV Kane, M Dubinsky, JD Lewis, S Degli-Espositi, WJ Sandborn, BE Sands & CCFA Alliance

- **Patients were divided into 3 groups:**
  - **Group 1: no immunomodulators/biologics**
    - (mesalamine, steroids, antibiotics allowed)
  - **Group 2: AZA/6MP**
    - +/- Group 1 medications
    - 2b: MTX, CSA, Tacrolimus
  - **Group 3: INF, ADA, CZP**
    - +/- Group 1, 2 medications
    - 3b: Natalizumab

# Drug Exposure by Trimester

	Preconception (n) 3 mo < LMP	T1 (n)	T2 (n)	T3 (n)
Group 1 n= 106	163	150	92	97
Group 2 AZA/6MP n=56	70	62	34	30
Group 3 Anti-TNF N=75	67	64	49	37

# Outcomes

Outcome	Incidence (N=237)	Rate (%)	National <sup>1</sup> Rate(%)
<b>SAB</b>	9	3.8	13-19
<b>Stillbirth</b>	0	0	.03
<b>Preterm</b>	25	10.6	18
<b>IUGR</b>	6	2.5	3-5
<b>LBW</b>	18	7.6	8.3
<b>C section</b>	104	43.9	25
<b>NICU</b>	28	11.8	5
<b>Cong Abnorm</b>	11	4.6	3
<b>Any Comp</b>	108	45.6	--

# **Certolizumab Use in Pregnancy: Low Levels Detected in Cord Blood**

U Mahadevan, MT Abreu

- **Inf is detected in cord blood and newborns. Because IgG1 is actively transferred across the placenta during the T3, newborn serum Inf levels are higher than maternal serum levels at birth**
- **Cimzia, a Fab' fragment against TNF-alpha, has been shown to have low placental transfer levels in a rat model**

# CERTOLIZUMAB LEVELS

Five patients have been identified to date. Two completed their pregnancies.

	Prior anti-TNF	Maternal Age (years)	Duration of CD (years)	CZP prior to pregnancy	# doses during pregnancy	Trimester used
<b>Pt 1</b>	<b>INF</b>	<b>22</b>	<b>8</b>	<b>No</b>	<b>&gt;4</b>	<b>T2, T3</b>
<b>Pt 2</b>	<b>INF (T1)</b>	<b>31</b>	<b>3</b>	<b>No</b>	<b>8 Induction</b>	<b>T1-3 PP</b>

	Interval: Last dose to delivery (weeks)	Maternal Level DOB ( $\mu\text{g/ml}$ )	Cord Blood Level DOB ( $\mu\text{g/ml}$ )	Newborn level DOB ( $\mu\text{g/ml}$ )	Neonatal complications
<b>Pt 1</b>	<b>2</b>	<b>18.8</b>	<b>1.65 (8.8%)</b>	<b>--</b>	<b>None: 37 wks 2700 gm</b>
<b>Pt 2</b>	<b>&lt; 1</b>	<b>59.57</b>	<b>0.94 (1.6%)</b>	<b>1.02 (1.7%)</b>	<b>None: 38 wks 1956 gm</b>

LOQ 0.41

**Miscellaneous**

# **Vitamin B12 Deficiency in Crohn's Disease: Oral Supplementation Is Effective**

S García López, S Gallego Montañes, F Gomollon, M Gracia Ruiz, R Vicente Lidón

- **1 mg of cobalamin per capsule PO**
- **The average value of vitamin B12 pre PO was 167 pg/ml (46-489) and 2-3 months later was 472.11 pg/ml (177-1369)**
- **The 2 failures of oral treatment were treated by intramuscular route**

# **Dietary Poorly Absorbed Short-Chain Carbohydrates (FODMAPs) Increase the Volume and Fermentable Substrate Content of Ileal Output**

JS Barrett, RB Gearry, PM Irving, JG Muir, ML Haines, PR Gibson

- Carbohydrates that are rapidly fermented and osmotically active
- n=12 with ileostomy and no evidence of small bowel disease- x2 four-day dietary periods, differing only in FODMAP content (high v low).
- High FODMAP diet increased daytime effluent collection weight by 22% (95% CI 5- 39%; p=0.01), This represents an increase in output of 950 (280-1610) ml over 14 h.