Division of General Medicine

Senior Medicine Rotation: Evidence-Based Medicine Project

SubI Name: Shannon Watkins Block: July 2008 Date: July 18,2008

Case signout: 23 year old woman a history of multiple admissions for fever and abdominal pain over the past year, with CT findings of terminal ileitis (likely Crohn's disease) presents now with complaints of abdominal pain and fevers to 103 F x 3 days. She has been in and out of the hospital at least 4 times over the past year, each time discharged on a steroid taper. She is maintained on mesalamine PO QID at home, but frequently relapses and returns to the hospital a few weeks after finishing her steroid taper.

Is there a better treatment strategy available than traditional corticosteroid therapy to treat active Crohn's disease?

Search Strategy

Database: Ovid/Medline

I. Search Strategy

#	Search History	Results
1	Randomized Controlled Trial	261457
2	random$.tw.	418853
3	random allocation.mp. or Random Allocation/	62821
4	1 or 2 or 3	523761
5	therapy.mp	1198798
6	treatment.mp. or Therapeutics/	2187985
7	5 or 6	2867167
8	4 and 7	236284
9	crohn's disease {No Related Terms}	1198
10	8 and 9	367

II. Search Results (Citation displayed, by relevance)

1. Camma C. Giunta M. Rosselli M. Cottone M. Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables.[see comment]. [Journal Article. Meta-Analysis] Gastroenterology. 113(5):1465-73, 1997 Nov.

UI: 9352848

2. Griffiths AM. Ohlsson A. Sherman PM. Sutherland LR. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. [Comparative Study. Journal Article. Meta-Analysis] Gastroenterology. 108(4):1056-67, 1995 Apr.

UI: 7698572

3. D'Haens G. Baert F. van Assche G. Caenepeel P. Vergauwe P. Tuynman H. De Vos M. van Deventer S. Stitt L. Donner A. Vermeire S. Van de Mierop FJ. Coche JC. van der Woude J. Ochsenkuhn T. van Bodegraven AA. Van Hootegem PP. Lambrecht GL. Mana F. Rutgeerts P. Feagan BG. Hommes D. Belgian Inflammatory Bowel Disease Research Group. North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial.[see comment]. [Journal Article. Multicenter Study. Randomized Controlled Trial] Lancet. 371(9613):660-7, 2008 Feb 23.

UI: 18295023

4. Sandborn WJ. Hanauer SB. Rutgeerts P. Fedorak RN. Lukas M. MacIntosh DG. Panaccione R. Wolf D. Kent JD. Bittle B. Li J. Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial.[see comment]. [Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Gut. 56(9):1232-9, 2007 Sep.

UI: 17299059

5. Schreiber S. Khaliq-Kareemi M. Lawrance IC. Thomsen OO. Hanauer SB. McColm J. Bloomfield R. Sandborn WJ. PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease.[see comment][erratum appears in N Engl J Med. 2007 Sep 27;357(13):1357]. [Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] New England Journal of Medicine. 357(3):239-50, 2007 Jul 19.

UI: 17634459

6. Sandborn WJ. Feagan BG. Stoinov S. Honiball PJ. Rutgeerts P. Mason D. Bloomfield R. Schreiber S. PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease.[see comment]. [Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, N.I.H., Extramural. Research Support, Non-U.S. Gov't] New England Journal of Medicine. 357(3):228-38, 2007 Jul 19.

UI: 17634458

7. Selby W. Pavli P. Crotty B. Florin T. Radford-Smith G. Gibson P. Mitchell B. Connell W. Read R. Merrett M. Ee H. Hetzel D. Antibiotics in Crohn's Disease Study Group. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease.[see comment]. [Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Gastroenterology. 132(7):2313-9, 2007 Jun.

UI: 17570206

8. Targan SR. Feagan BG. Fedorak RN. Lashner BA. Panaccione R. Present DH. Spehlmann ME. Rutgeerts PJ. Tulassay Z. Volfova M. Wolf DC. Hernandez C. Bornstein J. Sandborn WJ. International Efficacy of Natalizumab in Crohn's Disease Response and Remission (ENCORE) Trial Group. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. [Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Gastroenterology. 132(5):1672-83, 2007 May.

UI: 17484865

9. Hyams J. Crandall W. Kugathasan S. Griffiths A. Olson A. Johanns J. Liu G. Travers S. Heuschkel R. Markowitz J. Cohen S. Winter H. Veereman-Wauters G. Ferry G. Baldassano R. REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children.[see comment]. [Journal Article. Multicenter Study. Randomized Controlled Trial] Gastroenterology. 132(3):863-73; quiz 1165-6, 2007 Mar.

UI: 17324398

10. Chermesh I. Tamir A. Reshef R. Chowers Y. Suissa A. Katz D. Gelber M. Halpern Z. Bengmark S. Eliakim R. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. [Journal Article. Multicenter Study. Randomized Controlled Trial] Digestive Diseases & Sciences. 52(2):385-9, 2007 Feb.

UI: 17211699

***I tried to add in other search terms like placebo or control or corticosteroids or hydrocortisone or prednisone or immunosuppression, but the above listed search terms gave me the best search results

Featured Journal Article:

Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. 2008 Feb 23;371(9613):660-7.

BACKGROUND: Most patients who have active Crohn's disease are treated initially with corticosteroids. Although this approach usually controls symptoms, many patients become resistant to or dependent on corticosteroids, and long exposure is associated with an increased risk of mortality. This study aims to compare the effectiveness of early use of combined immunosuppression with conventional management in patients with active Crohn's disease who had not previously received glucocorticoids, antimetabolites, or infliximab.

Pathophysiology of Crohn's Disease: A chronic inflammatory disorder of the GI tract. Most common initial tx is corticosteroid therapy. Experts recommended steroids for short-term use (3 months) only but they are often needed chronically.

Glucocorticoids MOA: Immunosuppressant, prevents translation of pro-inflammatory genes

Azathioprine MOA: Immunosuppresant, pruine synthesis inhibitor

Methotrexate MOA: Antimetabolite, anti-folate

Infliximab MOA: TNF-a antagonist

Group	Criteria or definition	N
Population screened.	Patients from 18 centers in Belgium, Holland, and Germany between May 2001 and January 2004.	140
Inclusion criteria	1-Age 16-75 years old. With recent diagnosis of Crohn's disease within the past 4 years. No hx of previous treatment with corticosteroids, antimetabolites,, or biological agents 2-Pts had active disease = Crohn's disease activity index (CDAI) score of greater than 200 points for a minimum of 2 weeks before randomization	133
Exclusion criteria	1-Immediate need for surgery; symptomatic stenosis or ileal or colonic strictures with prestenotic dilation; signs, symptoms, or laboratory tests that indicated severe comorbidity; documented chronic infection; a positive stool culture for pathogens; a positive tuberculin test or a chest radiograph consistent with tuberculosis; or a malignancy. Also, any patient allergic to murine proteins, pregnant, or a substance abuser.	7 ineligible (3 CDA<200) (2 infxn enteritis) (2 immed sx)
Treatment group (early combined immunosuppresion)	Received three infusions of infliximab at weeks 0,2,6 + azathioprine constantly from day 0 onward. If pt responded (response = 50 pt d w/score 200-250; 75 pt d w/ 250-300; 100 pt d w/ >350) and tolerated regimen, azathioprine continued for duration of trial. If pt intolerant to azithioprine, pt given subQ methotrexate at 25 mg/week x 12 weeks, with 15 mg taper per week thereafter. If sxs worsened CDAI up > 50 pts, then pts given additional infliximab infusions. If sxs still persisted, methylprednisolone started and continued w/ azathioprine and methotrexate.	67
No treatment group (conventional tx) ***tx according to current guidelines of clinical practice	Induction with methylprednisolone (32 mg x 3 weeks w/ taper by 4mg per week) or budesonide (9 mg /day x 8 weeks, then taper by 3mg/d). If responsive, then steroid dose tapered (total tx time = 10 week course). If sxs worse during course, increased dose to initial dose, and repeat induction tx. If continued worsening, then azathioprine begun. Pts who relapsed after steroid taper were given a second course of steroids + azithioprine. Pts who failed 4 weeks of corticosteroid tx, increased dose methylprednisolone to 64 mg + azathioprine x 2 weeks w/subsequent taper of steroids. **any pt who was symptomatic s/p 16 weeks azathioprine tx got induction course of infliximab (wk 0,2,6) + continued antimetabolite tx **pts who were intolerant to both azathioprine and methotrexate also received infliximab w/o antimetabolite tx→w/relapse infusion of infliximab repeated	66

*****unethical to withhold a known and effective tx*****

Primary endpoints: Remission @ Wk 26 and Wk 52

1- CDAI score of less than 150 points in the absence of corticosteroid treatment, and no intestinal resection at wk 26 and 52. (Since LT steroids – bad SEs, and complete corticosteroid withdrawal – essential element of the clinical definition of remission).

Secondary endpoints:

1-Time to relapse (>200) after successful induction treatment(<150)
2-Mean CDAI and IBDQ scores
3-Mean concentrations of serum C-reactive
4-Proportion of patients in remission (CDAI <150 + no corticosteroid tx at wk 14)
5-Proportion of pts given infliximab, methylprednisolone, and antimetabolites anytime in the study
6-Proportion w/o ulcers after 24 months of treatment
7-Daily dose of methylprednisolone

Are the Results of the Trial Valid?

- Randomized? Yes
- All patients accounted for at end? Yes (14 withdrew from ECI group; 17 withdrew from Conv Management(by 2 yr f/up)
- Intention to treat? Yes
- Blinding? No, open study Both patients and doctors knew treatment groups (confounder bc pts may have a reporter bias given subj nature of CDAI and IBDQ though more objective markers CRP, ulcers on duodenoscopy also showed a real chage; another confounder is the placebo effect; Investigators also were aware of tx group which may have biased them in their assessment of efficacy, however as mentioned above objective markers of inflammation: CRP and mucosal ulceration were improved w early combined immunosuppresion)
- Groups similar at start of trial? Yes, randomized. Also minimization procedure employed to balance differences btwn treatment groups in prognostic factors (baseline CDAI score, tobacco smoking, disease location)
- Equal treatment of groups? Yes, except that some arms of the early immunosuppressive group received multiple pulses of infliximab. Some studies suggest intermittent infliximab use may be beneficial in itself; no arms of traditional treatment group received multiple courses of infliximab). Also, Early combined immunosuppresion group received both infliximab + AZA at initiation of the study, while Conventional group received Steroids x 4 weeks, followed by the initiation of AZA in those steroid refractory cases. Question of whether Traditional tx arm would have done better if tx initiated w/both steroids + AZA. However, AZA and MTHX have a slower onset of action so this is less likely to explain response. Also, this design was constructed so the convemtional treatment group would mimic principles of clinical practice.
- Did randomization work? Yes

***Overall, results of trial would be more valid if trial was double blinded bc of recall bias and placebo effect as mentioned above. A single or double blinded study would eliminate some of these biases. Also, investigator bias also must be considered. However, given that objective markers of inflammation (CRP and Mucosal Ulceration) improved in Tx group, this indicates that likely results of trial are valid in spite of the inherent biases of the study. Additionally, the slightly different handling of the two groups reflects clinical practice, so allows the study to address whether this new approach is superior to current clinical approaches.

Are the Results of the Trial important? Yes

- Size of treatment effect? Yes
- Precision of the estimate of the effect? Yes

Endpoint	Result	Significance	ARR	NNT
Primary: 1-Remission = CDAI score of less than 150 points in the absence of corticosteroid treatment, and no intestinal resection.	[14wk- 63%(E) vs 32%(C)] 26 wk-60%(E) vs35.9%(C) 52 wk-61.5%(E)vs42.2%(C) [78 wk-42%(E)vs45%(C) 104 wk-65%(E)vs55%(C)]	(14)P=0.001 (26)P=0.006 (52)p=0.028 (78)p=.797 (104)p=0.431	14(-31%) 26(-24.1%) 52(-19.4%) 78((-3%) 104(-10%)	3.2 4.2 5.15 33.33 10
Secondary: 1-Time to relapse (>200) after successful induction treatment(<150) 2-Mean CDAI and IBDQ scores 3-Mean concentrations of serum C-reactive 4-Proportion of patients in remission (CDAI <150 + no corticosteroid tx at wk 14) 5-Proportion of pts given infliximab, methyl prednisolone, and antimetabolites anytime in the study 6-Proportion w/o ulcers after 24 months of treatment 7-Daily dose of methylprednisolone	1-329(E) vs 174.5(c) 2-CDAI: E 231 drop vs C 178 drop; IBDQ: E 59.2 drop vs C 37.4 drop (At 10 wks) 3- ECIS: more rapid reduction of CRP levels in serum (-15mg/dl vs -4.2mg/dl) 4-E63% vs C 32% 5- E got more and longer course of antimetabolites, but by end of trial 76% of Conv gropu also got antimetabolite. Conv group got longer time of exposure vs ECIS to steroids. Similar proportion of pts using infliximab by the end.. 6-no ulcers on EGD(73.1% ECIS vs 30.4% C) 7- 0 mg(E) vs 35 mg ©	1-P=0.031 2-p = 0.0184; p = 0.0014 3-p=0.0244 4-p=0.001 5-p=0.0028 6-p=0.0028	 3-na 4—31% 5-46% 6--40%	 3-na 4-3.2 5-2.2 6-2.5
Morbidity	**Result**	**Significance**	**ARI**	**NNH**
Patients with a serious AE	30.8%(E) vs 25.3%(C)	P=1	5.5%	18.2
• *see attached table to	more adverse rxns….			

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- Can I apply these results to my patient? No, for a few reasons: 1-pt does not meet inclusion criteria at this time: Pt has a history of multiple failed courses of steroid tapers. These pts are first time tx. 2-Pt meets an exclusion criteria: a stool culture come back (+) for C.diff while in-house. ***However, could have applied to her on her first presentation to a hospital for a CD flare (CDAI was within range 325, IBDQ not known).
  - Comparison of my patient to trial patients. Yes: age, DAI.
  - All clinically important outcomes considered. Yes
  - Likely benefits outweigh potential harms and cost? Yes

**Note: At endpoint of remission (78-104 weeks) 76% of pts in conventional group were receiving anti-metabolites. This could explain why early immunosuppressive therapy no longer appears to be beneficial vs conventional therapy in remission rates at this time. Although no benefit is seen in wk 72 and 104, higher remission rates up until week 52 likely translate into less morbitity as measured by the CDAI and IBDQ and improvements in QOL. Also, it is important to remember that even though remeission rates appear the same at week 72 and later, the conventional group has had more total time exposure to steroids vs early immunosuppression. This is important bc long steroid courses have been clearly associated w increased morbidity and mortality. Additionally, those that do improve on ECIS have a longer time before relapsing again which is important as well.

APPENDIX:

The Crohn's disease Activity Index (CDAI): Validated survey that has been commonly used to assess CD severity

The CDAI was developed in 1976. It is an index that consists of eight factors, which are summed after adjustment by a weighting factor. The components of the CDAI and weighting factors are as follows:

Clinical Feature	Weighting factor	Pt
Number of liquid or soft stools each day for seven days	x 2	14
Abdominal pain (graded from 0-3 on severity) each day for seven days	x 5	35
General well being, subjectively assessed (0 (well)→4 (terrible) daily for seven days	x 7	14
Presence of complications*	x 20	40
Taking Lomitil or opiates for diarrhea	x 30	0
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	x 10	50
Absolute deviation of Hematocrit from 47% in men and 42% in women	x 6	114
Percentage deviation from standard weight	x 1	50

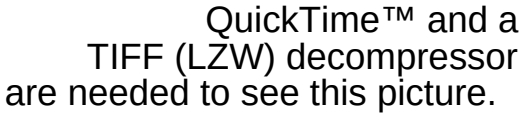
*One point each is added for each set of complications:

1- the presence of joint pains (arthralgia) or frank arthritis
2- inflammation of the iris or uveitis
3- presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
4- anal fissures, fistulae or abscesses
5- other fistulae
6- fever (> 100 °F) during the previous week.

My patient' approximate score = 317

IBDQ: Irritable Bowel Disease Questionaire

This is another validated survey that is widely used in clinical trials with IBD. It is used to assess Quality of Life in patients w/ IBD. The IBDQ is a 32-item questionnaire regarding quality of life in IBD. It measures QOL in different aspects of life: 1-emotional function (worried, feeling depressed, frustrated), 2-social function (function in leisure and work), 3-systemic symptoms (being tired, having sleep problems, lack of energy), and 4-bowel function (stool consistency, frequency, pain). Scores range from 32-224, with higher scores indicating a higher QOL.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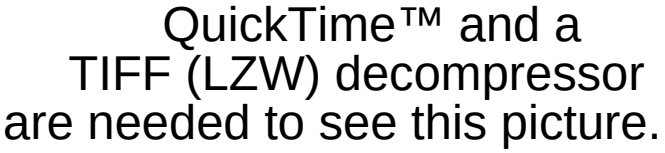
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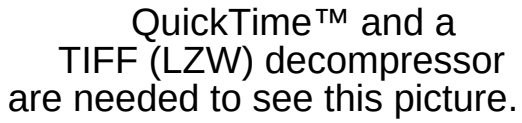
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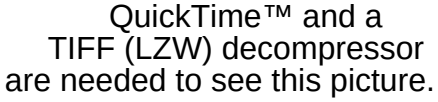
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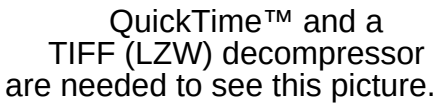
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