

Immune Ablation and HSCT, refractory Crohn's

6 year follow up

2001-2008

Remissions and Relapses

Randomized Trial Initiation

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Background. Theory

- Ablation of aberrant immune system, with elimination of auto-destructive T cells
- Reconstitution with new immune cells

Background HSCT

- Immune ablation vs. hemato-ablation
- Allogeneic vs. Autologous
- Some centers as high as 5 % mortality
- NUMS Mortality approximately 1%
 - Extensive experience HSCT
 - Immune ablation rather than Hemato-ablation

Methods-Subjects

- 16-40 years
- Failure standard therapy including TNFa-Ab
- CDAI 250-400
- Severity Index > 16
- Genetic defects: 3- Heterozygous TLR5
 - 1- Heterozygous NOD2

Methods - Mobilization Phase

- Cyclophosphamide 2gm/M²
- G-CSF 10 mcg/kg/day
- Peripheral blood leukapheresis
- CD34+ Immunoselection
- 2,000,000 cells/kg

Methods-Conditioning Phase

- Approximately 1 month later
- Cyclophosphamide 50 mg/kg/day 4 days
- ATG 30 mg/kg/day 3 days
- Mesna to prevent cystitis
- Methylprednisolone 1.0 gm/day of ATG
- Reinfusion of Stem Cells
- G-CSF daily until ANC 500/mcl

Randomized Controlled Trial

- Full HSCT
- vs Delayed (Mobilization only)
 - Conditioning if CDAI > 225 @ 1 Yr
- One subject enlisted
- Two others accepted, pending insurance
- Accession difficult
 - Insurance coverage
 - Competition other trials with Crohn's
 - Advertisements in progress

Results

- In hospital, 48 hours culture negative fever only morbidity
- In most, improvement in diarrhea and pain in hospital
- In most, cessation of immunosuppression and corticosteroids
- In most, gradual improvement
- QOL questionnaire improvement in each interval

Subject F, Pre HSCT

- May 2002, 27 year old woman
- Crohn's onset 1996, continuous disease
- Perianal fistulae, small bowel obstructing and perforating
- SB rsx 2000, 2001; ileocolostomy 2001
- Infliximab intolerance or failure 1999
- Continuous pain, HPN 8/01; 10 stools daily; eating little
- HSCT 12/02

Subject F, post HSCT

- Marked improvement immediately
- Fear of eating; gradual reduction TPN
- Remission
- Mild flare 2 years
- Resumption infliximab
- Remission in all respects 1/08 (5 years p HSCT)

Relapses and Surgery

- 9 subjects relapsed
 - 3 1/2 years 2
 - 2 years 4
 - 1 year 3
- Cigarette smoking resumption in 4
- 5 relapsing subjects required surgery
- More responsive to therapy post relapse
- All required resumption of corticosteroids and immunosuppression
- 3 required surgery, unrelated to relapse
 - Sigmoidectomy, bladder fistula
 - Ileal stricturing

Remission Definition

- Difficult to define
- Clinical courses fluid
- Best definition
 - CDAI < 150
 - CSI < 12
 - No corticosteroids
 - Minimal or no symptoms
- Kaplan-Meier plot not realistic.
 - Remission after relapse or surgery
 - Slow vs rapid entry into remission

Remission

- Six years: 1
- Five years 3
- Four years 4
- Three years 4
- Two years 4
- 6 months 2
- Just initiated 1
- Three remain in relapse

Figure 1. C D A I

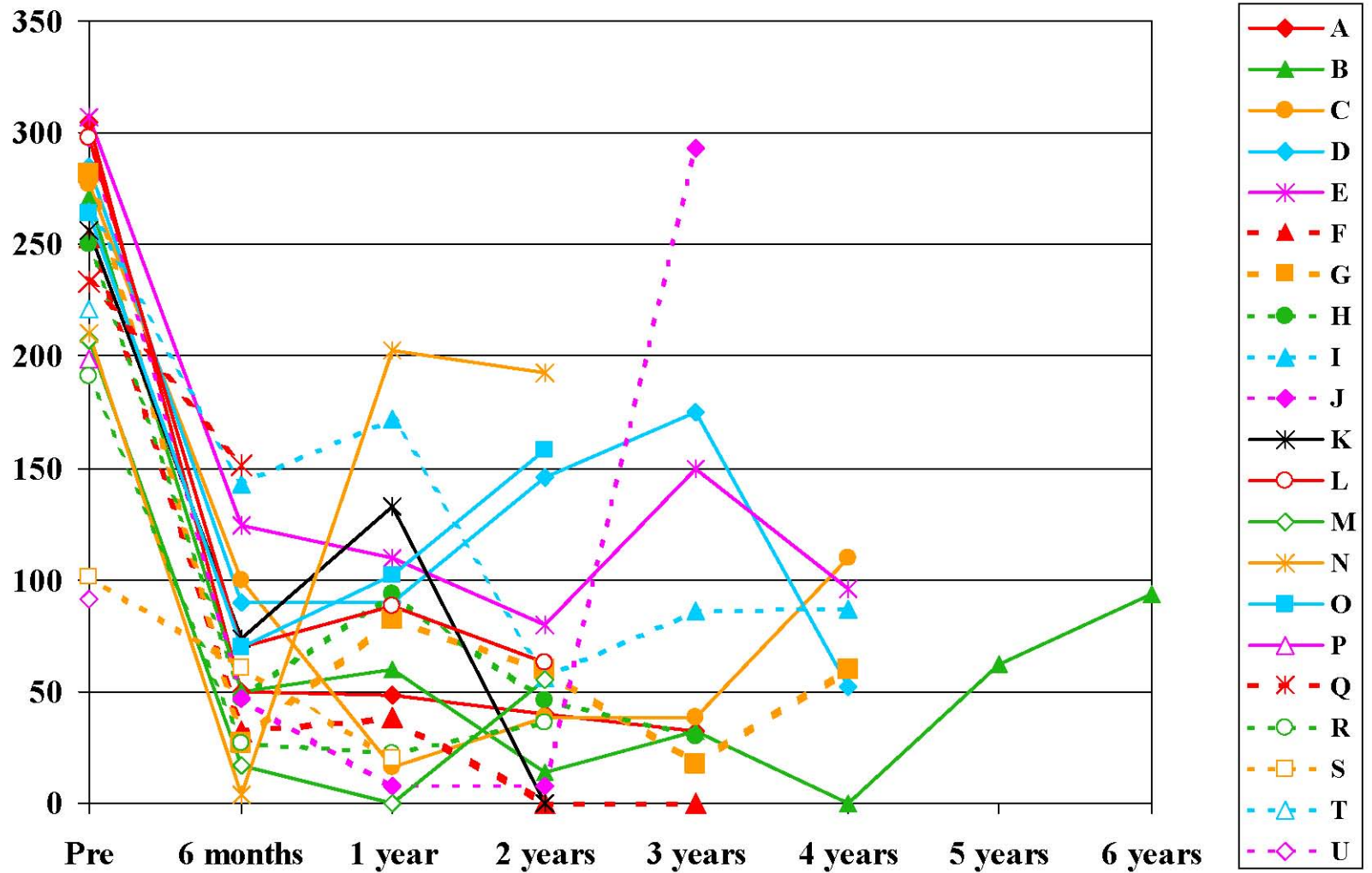
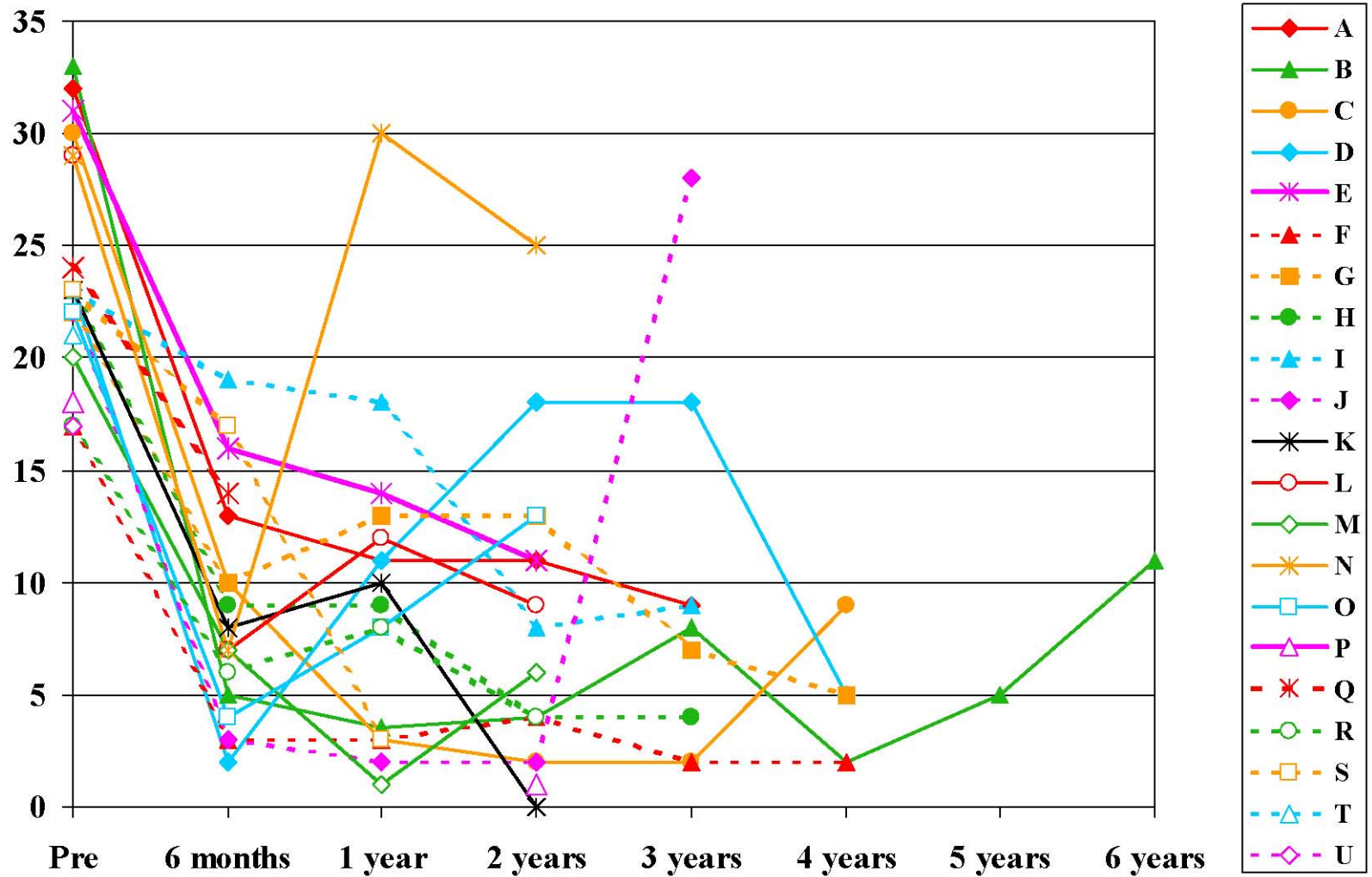


Figure 2. Crohn's Severity Index



HSCT Crohn's, Conclusions

- Can be performed safely in qualified BMT program
- Immune ablation with re-population with primitive stem cells
- May produce prolonged remission
- Response variable; 3 out of 22 relapsed and require continuing therapy
- Perianal disease may persist and require surgical management
- Fibrosing obstruction might worsen