

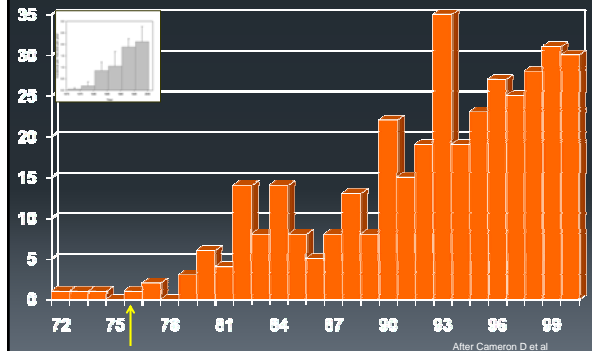
Crohn's Disease Treatment

Don Cameron

Grand Rounds RCH 27/07/2011

Newly diagnosed Crohn's - n=350

RCH & IMAC 1972 - 2000



Treatment options 1970s – 1980s

- Steroids
- Sulphasalazine
 - Side effects
- Antibiotics?
- Azathioprine - *with considerable hesitation*
- Diet - what?
- Surgery – *not if we could help it*
- Support
- Hope

Now

- Better understanding and use of Immunomodulators
- Enter the biologicals
- Nutrition
- Surgery
- Support
- Hope

Immunomodulators

- Thiopurines
 - Azathioprine
 - 6-Mercaptopurine
- Methotrexate
- Cyclosporine?
- Tacrolimus?

Thiopurines

Azathioprine, 6-Mercaptopurine

Explain risks

Immune suppression

Varicella, **check serology**, Immunise if necessary

Measure TPMT

Myelotoxicity – 7%, (3%/patient/year)

Hepatotoxicity – 5-10%

Pancreatitis – 3%

Flu-like syndrome, nausea, headaches

Lymphoma – 4:10,000

Dose AZA ~2.5 mg/Kg/d
6MP ~1.5 mg/Kg/d

Monitor FBE, LFTs, lipase

Thiopurines

Azathioprine, 6-Mercaptopurine

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Anti-TNF α treatment

▪ Infliximab (Remicade[®])

▪ original anti-TNF α

- 75% human, 25% mouse
- binds free and membrane-bound TNF α
- fixes complement and lyses CD4 and macrophages
- Down-regulates TNF α production

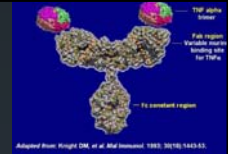
▪ Infusion at 0,2,6 weeks then 8 weekly

▪ Expensive – \$2,000 – \$5,000 per dose for drug only

- PBS subsidised
- Bureaucratic hoops

▪ Check for TB

▪ Update immunisations



RCH IBD infliximab patients

▪ >100 IBD patients treated since 2004 (mostly CD)

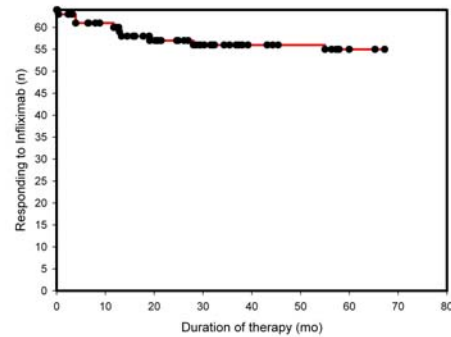
▪ *Episodic* until PBS funding from 2007

▪ *Maintenance* 8 weekly since 2007

▪ PBS regulations require "Bottom up"



Loss of response to IFX and treatment duration
(maintenance therapy group) (86% ongoing response to 67 mo)



Anti-TNF α treatment

▪ Adalimumab (Humira[®])

- Humanised
- Injection 2 weekly
- Expensive (comparable to Infliximab)
- Not PBS funded for Crohn's for <18 year olds

▪ Certolizumab

- Pegylated anti-TNF. Trial drug only.
- Preliminary results disappointing

Infliximab alert 2007 HSTCL

▪ 16* cases of Hepato Splenic T-Cell Lymphoma 2002 – 2007 (> 1million patients treated)

▪ All had had infliximab (1-24 doses), 2 also had adalimumab

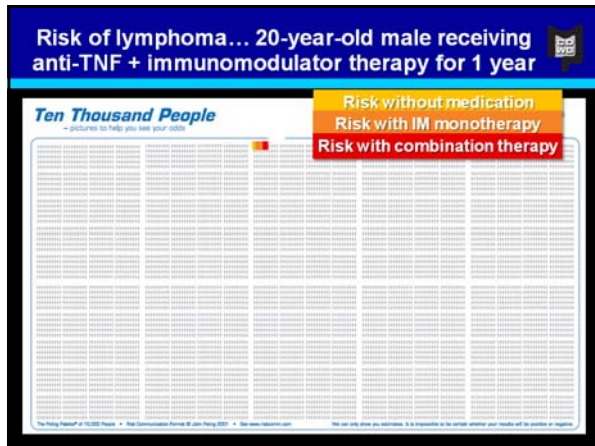
▪ Mostly young males

▪ All also on azathioprine or 6MP

▪ Fatal

▪ Current recommendation (may change) is to continue immunosuppression and review after 6 months on regular anti-TNF

* Now up to 36



- ### Newer treatments
- New biologicals directed at the inflammatory cascade
 - anti-TNF α preparations
 - inhibit recruitment of inflammatory cells
 - Natalizumab, selective adhesion molecule (SAM) inhibitor
 - block the signals
 - promote "good" cytokines
 - inhibit "bad" cytokines
 - ABT-874, human anti-IL12
 - Improve neutrophil function
 - Sargramostim
 - Enteral Nutrition
 - Helminthic therapy?
 - Anti-Mycobacterial therapy?

- ### 2011 and beyond
- ### Two lines of research
- New and better treatments
 - Cause and cure
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