Tolerisation Advisory Committee

Chris Barnes

Inhibitors in haemophilia

- Development of inhibitors most serious complication of haemophilia therapy
- Bypassing agents are available but haemostatic efficacy cannot match factor replacement in patients without inhibitors
- Immune tolerance therapy (ITT) is preferred (and most cost effective?) approach for patients with inhibitors

Immune tolerance therapy

- ITT
  - Three decades experience with different protocols
  - All protocols involve ongoing, uninterrupted exposure to FVIII / FIX (+/- immune modulation) over a period of weeks to months with the goal of producing antigen specific tolerance

Table I. Characteristics and outcome of reported ITI protocols.

ITI protocol	FVIII dose and associated treatment	Success rate (%)	Median time to success, months	Comments
Bonn protocol (high-dose regimen)*	FVIII 100–150 iu/kg every 12 h until inhibitor <1 BU, then FVIII 150 iu/kg until normalization of FVIII recovery and half-life.	92–100	14	Very demanding for patients. High cost
Malmö protocol (high-dose regimen + immune modulation)†	FVIII continuous infusion targeting plasma levels >30 iu/dl until negative inhibitor titre, then 60–90 iu/kg weekly + cyclophosphamide (i.v. 12–15 mg/kg days 1–2, 2–3 mg/kg orally days 3–10) + i.v. immunoglobulins 2·5–5 g/kg day 1, 0·4 g/kg days 4–8. Preliminary protein A sepharose immunoadsorption if initial inhibitor titre >10 BU.	59–82	1	Rapid response and cost-saving but need for hospitalization and concerns regarding the use of cyclophosphamide in children
Dutch protocol (low-dose regimen)‡	Neutralizing dose (25–50 iu/kg twice daily, 1–2 weeks), then tolerizing dose (50–75 iu/kg weekly)	61–88	1–12§	Less demanding for patients and cost-saving
Other low or intermediate dose protocols	Ewing *et al*, 1988: 50 iu/kg/d	67	2¶	Developed for improving cost-effectiveness of treatment
	Kucharski *et al*, 1996: 50 iu/kg/week	45	10	
	Unuvar *et al*, 2000: 50–100 iu/kg/d	57	6	
	Rocino *et al*, 2001: 100 iu/kg/d	75	8	

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Table II. Main features of published ITI Registries and predictors of ITI outcome.

Registry (reference)	Patients (severe)	HR, %	FVIII dose regimens (iu/kg/d)	Type of FVIII products	Success rate, %*	Time to success, months	Predictors of success (*P* value)†
International, IITR (Mariani & Kroner, 2001)	314 (263)	94	32% ≥200; 20% 100–199; 23% 50–100; 25% <50; steroids 7%	IP or HP plasma-derived 88%; recombinant 12%	51	10·5 (median)	Age at ITI start (0·008); pre-ITI inhibitor titre (0·04); historical peak titre (0·04); FVIII dose (higher, 0·03)‡
North-American, NAITR (DiMichele & Kroner, 2002; DiMichele, 2009)	164 (150)	78	14% ≥200; 33% 100–199; 28% 50–100; 25% <50; immune modulation 40%	IP or HP plasma-derived 25%; monoclonal or recombinant 75%	63	16·3 (mean)	Pre-ITI inhibitor titre (0·005); historical peak titre (0·04); peak titre on ITI (0·0001); FVIII dose (lower, 0·01)§
German, GITR (Lenk, 2000)	126 (109)	83	Most patients 200–300	IP or HP plasma-derived	76	7·6–15·5 (mean)¶	Historical peak titre (0·0012)**
Spanish Registry (Haya *et al*, 2001)	37 (35)	100	42% ≥200; 24% 100; 29% <100; 5% others; immune modulation 37%	IP or HP plasma-derived 88%; recombinant 12%	63	9·85 (median)	Pre-ITI inhibitor titre (0·03); historical peak titre (0·02); FVIII dose (lower, 0·01)**
Italian PROFIT study (Coppola *et al*, 2009)	103 (100)	96	Median 100 (range: 21–220)	IP or HP plasma-derived 24%; monoclonal 2%; recombinant 74%	53	8 (median)	Pre-ITI inhibitor titre (<0·001); peak titre on ITI (<0·001); *F8* mutation (non-null, 0·04)††

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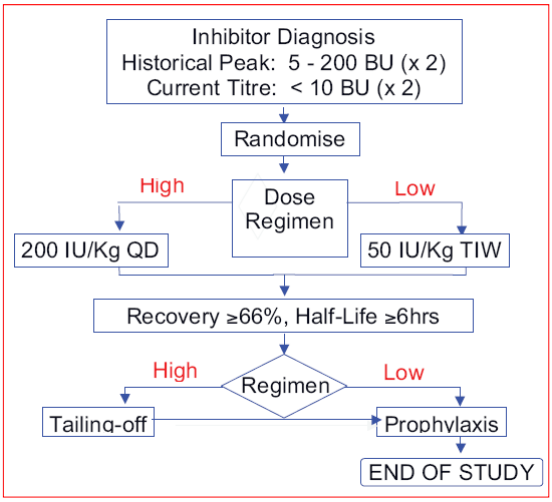
International immune tolerance trial



ITT guidelines

- UKHCDO, International consensus panel (ICP) and European consensus panel (ECP)
  - Deferring ITT until inhibitor titre < 10BU preferrable (level IIB or III)
  - Avoid FVIII prior to ITT (IIB)
  - Insufficient evidence to make strong recommendations regarding dose
  - No evidence to support superiority of individual product for ITT
  - VWF containing products should be considered in those patients who fail ITT (IIB)
  - Immune modulation is not recommended for first line therapy but should be considered for patients who have failed ITT

Immune tolerance therapy

- ITT
  - Important
  - Expensive
  - Difficult
  - Few reliable predictors of success available
  - Few patients available in each centre

Tolerisation Advisory Committee

- Developed in response to potential shortage of plasma derived clotting factor in Australia (Biostate); now less relevant
- Small numbers of patients at individual centers
- Process involved peer review of patients having tolerisation to provide general advice regarding tolerisation
- Monthly meetings via telephone conference
- Include review of any recent publications relevant to inhibitor management

Tolerisation Advisory Committee

- TOR
  - Provide a resource and advice on cases of immune tolerisation for patients with haemophilia and inhibitors in Australia
  - Encourage all cases of ITT in Australia to be reviewed by the TAC
  - To monitor the progress of cases of immune tolerance within Australia
  - To prospectively collect information in cases of immune tolerisation in Australia
  - To liaise with the supplying agencies regarding upcoming immune tolerisation cases
  - Encourage participation in trials involving cases of ITT

Tolerisation Advisory Committee

- Apply evidence based practice to ITT / management of patients with inhibitors
- ITT Discussion framework
  - Identify patients at standard risk vs high risk for ITT failure

Tolerisation Advisory Committee

- 35 cases referred
  - One case referred twice
- 34 cases haemophilia A
- 4 cases mild haemophilia A
- 5 cases low titre inhibitor (<5BU)
- Quality of data poor (role of ABDR?)

Audit of patients with inhibitors being treated with prophylaxis

- Data collection on patients having prophylaxis with bypassing agents
- Data collected 2010
- 9 patients with prophylaxis
  - Age range 2- 61 years

Audit of patients with inhibitors being treated with prophylaxis

HTC	Age	Product	Indication	Regime
RPAH	60.58	FEIBA	Reduce frequency of bleeds	100 u/kg 3 per week
RHH	28.46	FEIBA	Recurrent haemarthosis knee	64-51 u/kg 3 per week
CHW	17.92	FEIBA	Recurrent bleeds	100 u/kg 3 per week
CHW	5.74	FEIBA	Recurrent bleeds elbow	66 u/kg daily
RCHM	2.01	Novoseven	Prevent bleeds around port	100 mcg/kg for 22 days
RPH	69.30	Novoseven	Post orthopedic surgery*	90 mcg/kg 6/24 for 16 doses
RHH	4.76	Novoseven	Bleeding @ port site with infusions	100 mcg/kg 3 per week
CHW	3.39	Novoseven	Prophylaxis in ITT	100 mcg/kg daily

Audit of patients with inhibitors having surgery

- Data collected on patients with inhibitors having surgery
- 12 month calendar year
- 6 centres returned data

Audit of patients with inhibitors having surgery

- Age range 1.1 years to 88 years
- 16 surgical procedures
  - 5 port insertion / removal
  - 8 minor surgical procedures
  - Knee replacement
  - Bowel resection
  - TJ liver biopsy

Audit of patients with inhibitors having surgery

- 12 patients received Novo VII
  - 8 patients 90 – 100mcg / kg 2 hourly*
  - Range total dose 98 – 1000mcg*
- 4 patients (low titre inhibitor) received FVIII

Prophylaxis and Surgery Audits

- Prophylaxis for patients in Australia with inhibitors is rarely used but appears effective (particularly for short term secondary prophylaxis)
- Surgical procedures on patients with inhibitors in Australia regularly performed with relatively uniform peri-operative management strategy

Tolerisation Advisory Committee

- Provides platform for discussion of difficult cases against background of limited scientific evidence
- Now well established risk stratification of patients for ITT in keeping with international recommendations
- Developed collegial network for peer review of cases
- Timely collection of data in uniform fashion continues to be a challenge


AHCDO
• Thank you