

# Management of Reactions and Nerve Impairment

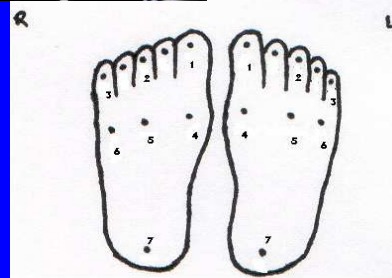
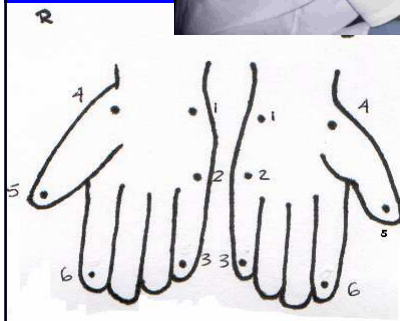
Dr Diana NJ Lockwood



## Nerve damage

- Occurs across the spectrum
- Occurs before diagnosis
  - Many patients present with new and old nerve damage
  - INFIR study showed that more sensitive tests detect more nerve damage
- During treatment
  - Reactions
- After treatment
  - Reactions
  - Late inflammation
  - Important to detect

## Neurological evaluation



## Classification of Reactions

- Type 1
- Neuritis
- ENL

Immune mediated events  
Treated with immuno-suppression  
Use as a tool for dissecting underlying  
reactional pathology

## Definition of T1R & neuritis

- T1R
- Skin
  - erythema & oedema of lesions,
  - new lesions
- Nerves
  - pain, tenderness
  - Loss of nerve function
    - VMT
    - Sensory testing (MF)
    - Importance of establishing that the nerve function loss is new

## Type 1 reaction or NFI- Published incidence rates

- |                          |              |
|--------------------------|--------------|
| • Hyderabad              | 8.9%         |
| • Orissa                 | 10.7%        |
| • <b>Ethiopia</b>        | <b>16.5%</b> |
| • <b>Bangladesh (MB)</b> | <b>17%</b>   |
| • <b>INFIR (MB)</b>      | <b>19.8%</b> |
| • <b>Thailand</b>        | <b>20%</b>   |
| • Hyderabad              | 24%          |
| • Chandigarh             | 24.1%        |
| • Nepal                  | 30%          |
| • <b>Malawi (MB)</b>     | <b>36%</b>   |

## Diagnosing T1R and neuritis

- Field/Clinic
  - Identify as many people as possible
  - High sensitivity
- Research
  - Identify only those people with T1R/Neuritis
  - High specificity
- INFIR Study
  - divergence between pathologist and clinician
- Clinical Severity Score
  - Useful tool for assessment and monitoring
  - Undergoing validation
  - Trials more comparable

## Prednisolone for Treating reactions

- 30-60 mg as starting dose
- 12-24 weeks treatment time
- WHO recommended
  - 40mg starting dose reducing over 12 weeks
  - Not supported by data from studies
  - 2006 WHO Operational Guidelines state 12- 24 weeks steroids

## Evaluating steroids

- Few randomised controlled trials
- Cochrane Review- only 3 trials met review criteria
  - Evidence from randomised controlled trials do not show a significant long term effect
- Different steroid regimens
- Different methods of evaluation
- Review the data from prospective studies

### Prospective studies using steroids in type 1 reactions and/or nerve function impairment

Author Year Country	Type of study	Entry criteria	Number enrolled	Intervention	Outcome measures	Conclusion
Touw-Langendijk 1984 Ethiopia	Open, uncontrolled	Recent nerve function loss	36	6 month course of prednisolone	Sensory and motor function	63% of affected nerves "improved" (59/93)
Kiran 1985 India)	?Prospective Open, uncontrolled	Impaired VMT or ST	33	Semi- standardized prednisolone regime	Nerve score	Good result in 74% of nerves
Schreuder 1998 Thailand	Observation study	Newly diagnosed leprosy patients	640	Not clear	Nerve function	Nerve damage at presentation improves in only 44% compared to 82% improvement in damage developing whilst on treatment
Croft 2000 Bangladesh	Prospective, open, uncontrolled	NFI	132	16 week standard prednisolone regime	Improvement	67% of nerves improved
Saunderson 2000 Ethiopia	Prospective field observation study	Neuropathy including nerve tenderness	594	Steroid regimes for 294 PB patients (12 weeks) and 300 MB (24 weeks) patients	Motor and sensory testing and symptom improvement	72% of all neuropathy given steroids responded fully

### Prospective studies using steroids in type 1 reactions and/or nerve function impairment

Author Year Country	Type of study	Entry criteria	Number enrolled	Intervention	Outcome measures	Conclusion
van Brakel 2003 Nepal, Bangladesh	Randomized placebo controlled, double blind	Isolated mild sensory impairment	75	16 week standard prednisolone regime	Improvement in monofilament scores.	No difference between treated and untreated groups.
Richardus 2003 Nepal, Bangladesh	Randomized placebo controlled, double blind	NFI of 6-24 month duration.	92	16 week standard prednisolone regime	Sensory and motor test scores	No difference
Marlowe 2004 Nepal	Randomized, controlled	Type 1 reactions skin or skin and nerve	40	Azathioprine and prednisolone compared to 12 weeks prednisolone alone	Skin signs, nerve tenderness, sensory and motor testing and amount of extra prednisolone required	Equally effective
Rao 2006 India	Double-blind randomized controlled, parallel group	"Severe" type 1 reactions	334	3 prednisolone regimes: 3.5g over 5 months 2.31g over 5 months 2.94g over 3 months	Amount of extra prednisolone required	The 5 month regimes were equally effective and less additional prednisolone was required by these two groups than by the 3 month group

## Why longer steroid courses might be better

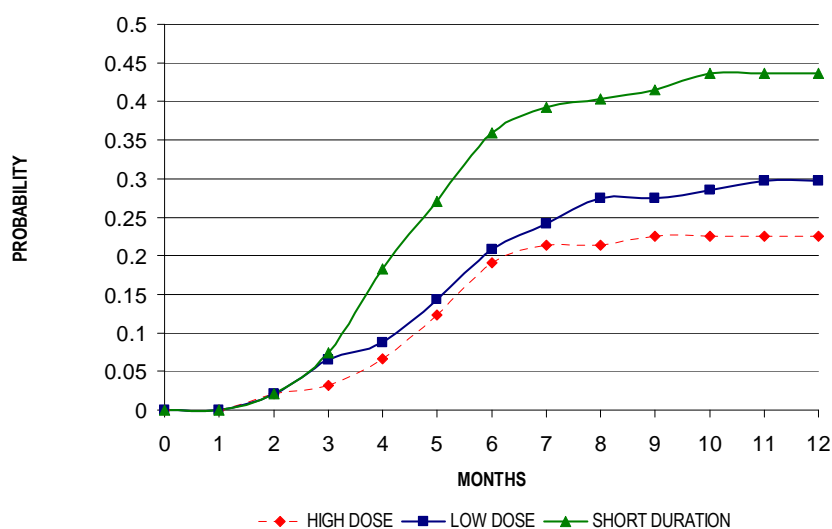
- Hyderabad study
  - cytokine profiles in BT/BL in reaction
  - 30mg 6 months steroids
  - 6 months BL patients still had high levels of pro-inflammatory cytokines (IFN $\gamma$ , IL-12, iNOS)
- Nepal Study
  - Comparing WHO regimen against Pred/Azathioprine
  - recurrence rate 30%

## Indian study

- 3 combinations of prednisolone
  - high, long 60mg → 5mg over 20 weeks
  - high, short 60mg → 5mg over 12 weeks
  - low, long 30mg → 5mg over 20 weeks
- Randomised controlled trial 268 pts
- Outcome: new symptoms requiring steroids within 12 months
- Best outcomes with longer treatment
- Poor performance of high, short regimen

Rao PS, Sugamran DS, Richard J, Smith WC. Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy. *Lepr Rev.* 2006; 77: 25-33

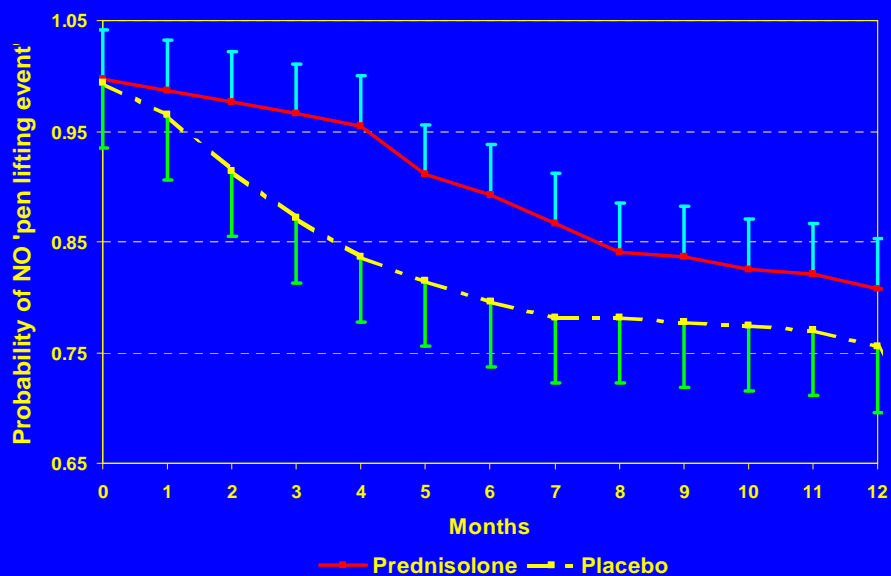
## Probability of needing extra steroids- Indian study



## New Approaches

- Can reactions be prevented?
- Tripod study- randomised MB patients to prednisolone 20mg or placebo daily first 4 months MDT

## Time to Reaction/NFI event



## Preventing Reactions

- Outcome
  - surprising
  - implies that reactional pathology is difficult to switch off
  - Disincentive to further prophylaxis studies

## Established immunosuppressants

- Define the use of second line drugs
- **Azathioprine and Prednisolone**
  - pilot study in Anandaban hospital, Nepal
  - 40 patients randomised to either Pred alone or a combination Pred/Aza 12 weeks
  - Pred/Aza combination as good as Pred alone and patients had less prednisolone
- Role for azathioprine as a steroid sparing agent
- RCT comparing pred and aza combinations over 24, 36 and 48 weeks started in India in Aug 2007. Placebo controlled

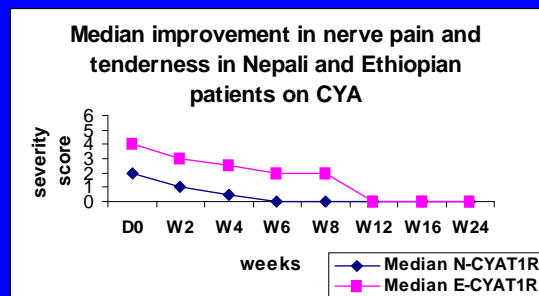
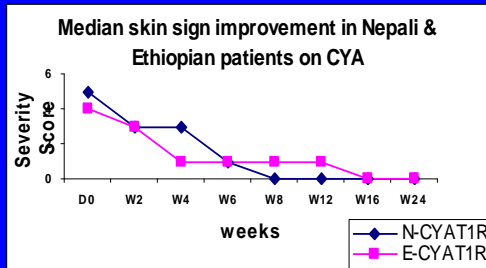
## Leprosy in Ethiopia



## Cyclosporin A in TIR

- Nepal (n=10) and ALERT (n=33)
- 12 weeks of CyA at 5mg/kg/day
- Skin signs improved in 88% Nepalis and 85% Ethiopians.
- Nerve Pain & Tenderness improved in 75% Nepalis & 45% Ethiopians.
- Relapses (skin)
  - 42% Ethiopian, 30% Nepali

## Skin and nerve evaluations on Cyclosporin therapy



## Cyclosporin A in T1R

- CyA levels – Ethiopians required higher doses
- Adverse Effects
  - Nepalis - Jaundice (1), ↑ Creatinine (1)
  - Ethiopians – HT (1)
- Conclusion
  - Clinical improvement
  - Need longer course
  - Further studies

## Methylprednisolone Study

- Methylprednisolone at 1gm per day for 3 days is effective in inflammatory conditions (RA, MS)
- Low side effect profile
- Phase 2 study in Anandaban Hospital, Nepal,
  - 40 patients randomised to MP or placebo.
  - Recruitment completed in Dec 2007.
  - Results end 2008
  - Low incidence of adverse effects in both groups, Data still blinded
  - Need for hospital admission was a disincentive for patients

## Treatment of Type 1 reactions conclusions - 1

- Steroids will remain the first line therapy
  - Widely available
  - Staff experienced in using them
- Better evidence to guide our practice
  - Now some RCT data
  - need better data
  - Need comparable studies in Asia, S America, Africa
  - Some patients have self healing
- Identifying patients at high risk of developing new damage
- Outcomes
  - Better definitions and comparable
  - Nerve Function and Skin improvement

## Treatment of Type 1 reactions conclusions - 2

- Define optimum dose and duration
- Long courses for best outcomes
- Second line drugs
  - Azathioprine, Cyclosporin, Methylprednisolone
  - ? methotrexate
- Side effects
  - Comparable data
  - Likely to differ between countries

## Operational research

- Recognition of reactions
- Patients to referral centres
- Drugs at referral centres
- Monitoring

## Collaborators

- BPRC
  - Sujai Suneetha
  - Indira Nath
- TLM India
  - Sundar Rao
  - Susheel John
  - Ruchika Mehindratta
- ALERT
  - Ruth Lekassa
- Anandaban Hospital
  - Rachel Hawksworth
  - Murdo Macdonald
- INFIR study
  - Cairns Smith
  - Wim van Brakel
  - Peter Nicholls
  - Einar Smith
- LSHTM
  - Steve Walker
  - Indira Kahawita
  - Jason McKnight
  - Sharon Marlowe

## Funders

- Lepra- UK
- Homes & Hospitals of St Giles, London
- Special Trustees, Hospital for Tropical Diseases, London
- Follereau Luxembourg
- ALM, USA
- Moulton Trust, UK
- TLMI
- Glaxo-Wellcome. UK