Erythema Nodosum Leprosum
ILC meeting Brussels Sept 2013

Diana Lockwood
Erythema Nodosum leprosum

• ENL still a challenge
• Clinically
• Pathologically
• Management
• Economics
• New network
• Challenges to take home
Erythema Nodosum Leprosum (ENL)

- LL and BL. Globally about 30,000 patients at risk of developing ENL
  - Referral centres, up 50% LL patients,
  - Under-diagnosis (INFIR study)
  - Every centre has a few patients with ENL - multi-faceted burden

- Chronic recurrence with immuno-suppression

- Hyderabad BPRC cohort
  - Acute, chronic, recurrent
  - Average time with ENL 2.4 years

- Audit Hosp Trop Dis, London some patients have ENL for 10 years
Clinical features of ENL
Erythema Nodosum Leprosum (ENL) Pathogenesis

• Immune-complex mediated
  – vasculitis
• Macrophage activation
• Recurrences
• What initiates ENL. What drives it?
Prednisolone requirement of patient with ENL

Weeks since diagnosis of ENL

- Total weekly dose of prednisolone
- Daily dose of thalidomide

Episode of neuritis

ENL
ENL Management

- Steroids
- Clofazimine
- Thalidomide
- Cochrane review (Van Veen 2009)
- Comprehensive review (Walker & Lockwood 2007)
- Other agents
  - Methotrexate, TNF inhibitors, Azathioprine, Ciclosporin, Pentoxyfylne.
Cochrane Review: Interventions for Erythema Nodosum Leprosum
Van Veen, Lockwood, van Brakel, Ramirez, Richardus 2009

- Cochrane review 13 studies (445 participants)
  - Steroids, thalidomide, clofazimine, pentoxyfylline, betamethasone, Indomethacin, levimasole.
  - 2002-7 - 3 studies

- Methodological problems
  - Absence of scales
  - Poorly defined endpoints
  - Selective reporting of data
  - No data on follow-up
  - Not analysed by intention to treat

- Conclusions
  - Thalidomide produced significant remission of skin lesions cf aspirin
  - Clofazimine superior to prednisolone (1 trial 24 participants)
  - Counter to clinician experience
• Very little data
• Most studies look at acute symptom control
• Major problem is preventing further episodes
• Chronic steroid use produces adverse effects
• Variable presentation
• Improvement over time
  – Apparent improvement may be due to spontaneous resolution
Clofazimine

- Weak immuno-suppressive
- Clofazimine vs placebo (Helmy 1971)
- Clofazimine vs Thalidomide (Iyer 1976)
- Clofazimine vs prednisolone (Ing 1969)
- Data only recorded for 4-6 weeks
- Time to next clinical episode not reported
- Adverse effects not reported
- 296 BL/LL patients followed in Cebu clinic
  - 12 or 24 mo MDT
  - Occurrence of ENL similar
  - Severity less in 24 mo but also associated with initial BI (>4)
• Discovered in 1954, withdrawn from markets in 1961
• Angiogenesis, immune function, inflammation, Inhibits growth factors (insulin).
• Rapid action, prevents recurrences
• Few side effects
  – Drowsiness, constipation, neurotoxicity
• 8 controlled studies, 3 since introduction of MDT
  – Villahermosa 2005, compared doses of Thalidomide
  – Sales 2005, compared Thalidomide vs Pentoxifylline
  – Kaur 2009 compared Thalidomide vs prednisolone
• Only 1 study comparing Thalidomide versus prednisolone
• Further study being presented here
• In Ethiopia (mortality in patients treated with steroids alone 8% )
# Case reports of Azathioprine in ENL

Immuno-suppressant, no RCT data

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Age/Sex</th>
<th>MDT</th>
<th>Pred Dose</th>
<th>Aza dose</th>
<th>Other Drugs</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>India</td>
<td>15 F</td>
<td>√</td>
<td>Pred 90</td>
<td>100</td>
<td>Thal, Clof</td>
<td>Prevented recurrence</td>
</tr>
<tr>
<td>2003</td>
<td>India</td>
<td>43 M</td>
<td>√</td>
<td>Pred 50</td>
<td>50</td>
<td>Ibuprofen, indomethacin, Chloroquine, Clofaz</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 F</td>
<td>√</td>
<td>Pred 80</td>
<td>50</td>
<td>Clofaz, Colchicine, Zn sulphate, Pentoxyfylne, Chloroquine,</td>
<td>Glaucoma, osteoporosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 F</td>
<td>√</td>
<td>Pred 60</td>
<td>50</td>
<td></td>
<td>Asymp after 3rd pulse</td>
</tr>
<tr>
<td>2007</td>
<td>India</td>
<td>53 F</td>
<td>√</td>
<td>Pred 40</td>
<td>50</td>
<td>Clofaz, Dexam</td>
<td>I more ENL episode then symp after 8 wks Aza</td>
</tr>
<tr>
<td>2011</td>
<td>Brazil</td>
<td>23-50</td>
<td>Some</td>
<td>30-100</td>
<td>100-150</td>
<td></td>
<td>5 ↓ Pred 50% by 12wks, 1 by 16 and 1 by 32 wks</td>
</tr>
</tbody>
</table>

Significant adverse effects when azathioprine used in India for T1R study
Ciclosporin in ENL

• Immuno-suppressant, acts on CD4 cells, inhibiting prod IL-2 and IL-4
• Inflammatory conditions- Psoriasis, RA, Inflamm Bowel Disease, Behcet’s
• Preventing transplant rejection

• No RCT’s. Only 4 case reports USA, suggested good outcomes

• Pilot study done in Addis Ababa, recruited patients with acute and Chronic ENL in separate studies. (Lambert et al)
• Initial data on 16 and 16 patients shows that Azathioseprine is useful in ENL, reducing time to relapse and severity.
Note: This material appears to be a presentation slide rather than a document, possibly from a medical or educational context. It discusses the use of TNF inhibitors for ENL (Erythema Nodosum Lymphocytic), with references to clinical cases from The Netherlands in 2006 and Canada in 2011. The presentations mention the use of Infliximab, Thalidomide, Prednisolone, and Etanercept, among other treatments, and highlight outcomes such as ENL improvement and recurrence. The discussion includes potential benefits and risks associated with these treatments, particularly concerning TB (Tuberculosis) and costs. The slide does not provide specific patient data or clinical outcomes beyond these general descriptions.
• Second line agents
  – Methotrexate, Azathioprine, TNF inhibitors.
  – All need assessing in larger studies using validated scales
  – The study from Ethiopia validates this approach
  – Cyclosporine initial data from Addis Ababa suggest that it is not useful in acute ENL
ENL Management

- WHO Expert Committee Report 2012
  - Prednisolone, clofazimine
  - Thalidomide
    - Can be used under strict medical supervision in specialised referral facilities
- ILEP Guideline Technical Bulletin (April 2011) Severity - Mild or severe
  - Steroids 30-60 mg/day reducing rapidly to 20mg
  - Clofazimine 300mg /day for 3-6 months
  - Thalidomide 400mg /day
  - Pregnancy prevention
Erythema Nodosum Leprosum International Study (ENLIST) Group – collaborating centres

- London School of Hygiene and Tropical Medicine
  United Kingdom

- Anandaban Hospital
  Kathmandu
  Nepal

- Leonard Wood Memorial Center
  Cebu
  Philippines

- Purulia Leprosy Mission
  West Bengal
  India

- Instituto Lauro de Souza Lima
  Bauru
  Sao Paolo
  Brazil

- Oswaldo Cruz
  Rio de Janeiro
  Brazil

- ALERT/AHRI
  Addis Ababa
  Ethiopia

- Bombay Leprosy Project
  Mumbai, India

- Leprosy Mission RC
  New Delhi, India
ENList

1. collect prospective individual patient data on the clinical features of ENL and treatment in leprosy referral centres in the ENLIST Group
2. To perform a physician global assessment of ENL activity at enrolment.
   • Patients newly diagnosed with ENL
   • Patients with recurrent ENL
   • Patients with Chronic ENL

Standardized definitions for each Clinical features - standardized
ENL Studies

• Quality of Life measurements
• Economic assessment
  – 2013 Survey on household expenditure in families with patients with ENL. 37% families surveyed tipped into catastrophic expenditure
    – Individual
    – Service providers
Future for ENL

• Need to build on WHO Expert Cmtee recomm make Thalidomide available
  – Working with regulatory authorities
• Need second line drugs
  – Established immuno-suppressants
  – Define role for TNF inhibitors
• Define pathogenesis
  – Risk factors genetic studies
  – Identify key pathway develop new drugs
• ENLIST will facilitate ENL research
Thanks

• ALM
• Hospital for Tropical Diseases, London
• Homes & Hospitals St Giles, London UK