THALIDOMIDE USE IN BRAZIL

INTRODUCTION

• 1956 – Commerce starts
  • Anti-nauseas for pregnancy
  • Sedative
  • Free sale

• 1961 – Teratogenicity
  • 12,000 children
  • Focomelia

• Withdrawal from the market
• It is possible that some of the originally reported cases of ´thalidomide embryopathy` were not due to thalidomide.

• In the 1990s, as the victims of the 1959-1962 disaster entered the reproductive age, cases of similarly affected children of thalidomide-damaged people were reported.

• Since it has been demonstrated that thalidomide is not a mutagen, according to Castilla et al (1996), these ´second generation cases` suggest that some of the original cases were misdiagnosed and actually represent a genetic syndrome with autosomal dominant traits.
ERYTHEMA NODOSUM LEPROSUM

• 1963: Sheskin found a great benefit to ENL after prescribing thalidomide as a sedative
• 1965: reported the result of five other ENL patients that were treated with thalidomide → all presented a rapid resolution or improvement of their lesions
• After that thalidomide began to be widely used to treat ENL
• In the late 1960s: it has been considered as a first choice drug to treat ENL, in Brazil

CURRENT USES (PARTIAL OR TOTAL CURE RATES)

DERMATOLOGY (anti TNF α)

• ENL (70-99%)
• GVHD (Graft versus Host Disease) (20-88%)
• Lupus erythematosus (84-100%)
• Sarcoidosis (83%)
• Scleroderma.
• Actinic prurigo (88%)
• Prurigo nodularis
• Aphthous Ulcers in HIV+ patients (50%)

• Erythema multiform
• Erosive lichen planus
• Lichen planopilaris
• Uremic pruritus (57%)
• Pyoderma gangrenosum.
• Jessner's lymphocytic infiltration (84%)
• Adult Langerhans cell histiocytosis
• Oral erosive lichen planus
CURRENT USES (PARTIAL OR TOTAL CURE RATES)

MALIGNANCY (anti angiogenesis)

- Multiple Myeloma (25-93%)
- Waldenstrom's Macroglobulinemia (25%)
- Myelodysplastic Syndromes (31%)
- Acute Myeloid Leukemia
- Myelofibrosis with Myeloid Metaplasia
- Renal Cell Carcinoma (0-17%)
- Malignant Gliomas (5-6%)
- Prostate Cancer (15-51%)
- Kaposi’s Sarcoma (35-40%)
- Colorectal Carcinoma (29%)
- Hodgkin's disease
- Small-cell lung cancer
- Unresectable hepatocellular carcinoma
- Cancer cachexia

Sampaio, E et al; Thalidomide:An overview of its Pharmacological Mechanisms of action; Anti-inflammatory & Anti-Allergy Agents in Medicinal Chemistry, vol 5 n1, 2006
CURRENT USES (PARTIAL OR TOTAL CURE RATES)

MISCELLANEOUS (both)

- HIV/AIDS-Associated Wasting
- Tuberculosis
- Reflex sympathetic dystrophy
- Systemic-onset juvenile rheumatoid arthritis.
- Adult-onset Still's disease
- Rheumatoid arthritis (20%)
- Pain inhibition

- Seronegative spondylarthropathy
- Periodontitis
- HIV-infected patients with refractory microsporidiosis.
- Behcet's Disease.
- Crohn's Disease (50%)
- Idiopathic colitis and proctitis (in HIV-Infected patients)

*Sampaio, E et al; Thalidomide:An overview of its Pharmacological Mechanisms of action; Anti-inflammation & Anti-Allergy Agents in Medicinal Chemistry, vol 5 n1, 2006*
SIDE EFFECTS

- **Serious**
  - TERATOGENICITY

- **Common**
  - SEDATION
  - PERIPHERAL NEUROPATHY
  - THROMBOEMBOLISM

- **Uncommon**
TERATOGENICITY
BRAZILIAN LAW (RDC 36/2011)

- File of prescribers and users
- Special form to prescribe (higher control)
- Report of side effects mandatory
- Orientation about discharge of left pills
- Criminal responsibility for misuse
Regulation of prescription

• Prescription only allowed for conditions listed by ANVISA (Brazilian regulatory agency)

• Prescription only allowed by physicians subscribed in a medical board

• Prescription form is special and must to be followed by a report to ANVISA accompanied by a Consent form

• Prescription for women in reproductive age has to follow
  • Medical evaluation
  • Exclusion of pregnancy with a sensitive test
  • Proof of two different contraceptive method (injectible and barrier or another definitive methods like tube tied)
OBJECTIVE

Evaluate the therapeutic course of prescription and use of Thalidomide in an urban area in northeastern Brazil.
SPECIFIC OBJECTIVES

• Identify the criteria used in prescribing thalidomide
• Identify the main clinical indications for thalidomide prescription
• Analyze of awareness about adverse effects of thalidomide by female users.
METHODS

• Descriptive, cross sectional study developed at the city of Fortaleza, Ceará, in four secondary and tertiary health care centers.

• Males and females from all age groups taking thalidomide were included in the study.
Thalidomide prescription by sex

- **Masculino**: 356 (70.1%)
- **Feminino**: 152 (29.9%)
### Thalidomide prescription by clinical indication

<table>
<thead>
<tr>
<th>Clinical Indication</th>
<th>Nº</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENL</td>
<td>353</td>
<td>69,5</td>
</tr>
<tr>
<td>Multiple Mieloma</td>
<td>96</td>
<td>18,9</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>21</td>
<td>4,1</td>
</tr>
<tr>
<td>Lupus</td>
<td>15</td>
<td>3,0</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>6</td>
<td>1,2</td>
</tr>
<tr>
<td>Prurigo</td>
<td>4</td>
<td>0,8</td>
</tr>
<tr>
<td>AIDS</td>
<td>3</td>
<td>0,6</td>
</tr>
<tr>
<td>Cutaneous Lymphoma</td>
<td>2</td>
<td>0,4</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>1,6</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>508</strong></td>
<td><strong>100,0</strong></td>
</tr>
</tbody>
</table>
Thalidomide prescription by health unit

![Bar chart showing thalidomide prescription by health unit]

- Others
- Oncology Center
- Primary Care Unit
- Private Dermatology Unit
- Private Hematology Unit
- General Hospital
- Institute of Cancer
- CDERM

The chart shows the distribution of thalidomide prescriptions across different health units.
Thalidomide prescription by prescriber

- General Practitioner
- Infectologist
- Rheumatologist
- Leprologist
- Family Doctor
- Oncologist
- Hematologist
- Dermatologist

Thalidomide prescription by prescriber:
- General Practitioner: 17.6%
- Infectologist: 26.5%
- Rheumatologist: 29.4%
- Hematologist: 29.4%
- Oncologist: 17.6%
- Leprologist: 26.5%
- Family Doctor: 29.4%
- Dermatologist: 29.4%
### Socioeconomic characteristics of thalidomide users

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>10</td>
<td>10,6</td>
</tr>
<tr>
<td>Incomplete elementary school</td>
<td>48</td>
<td>51,1</td>
</tr>
<tr>
<td>Complete elementary school</td>
<td>24</td>
<td>25,5</td>
</tr>
<tr>
<td>High school</td>
<td>12</td>
<td>12,8</td>
</tr>
<tr>
<td><strong>Family income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 minimal wage</td>
<td>14</td>
<td>14,9</td>
</tr>
<tr>
<td>1 to 4 minimal wage</td>
<td>75</td>
<td>79,8</td>
</tr>
<tr>
<td>&gt; 4 minimal wage</td>
<td>5</td>
<td>5,3</td>
</tr>
</tbody>
</table>
Contraception among thalidomide female users (10-49 years old)

<table>
<thead>
<tr>
<th>Pregnancy test</th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>9</td>
<td>45,0</td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>55,0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraceptional method use</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>17</td>
<td>85,0</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>15,0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraceptional method</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable Anticoncepcional</td>
<td>6</td>
<td>35,3</td>
</tr>
<tr>
<td>IUD</td>
<td>1</td>
<td>5,9</td>
</tr>
<tr>
<td>Tube tied</td>
<td>8</td>
<td>47,0</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>11,8</td>
</tr>
</tbody>
</table>
CONCLUSION

- The disaster of thalidomide brought an unprecedented advance to pharmacology.
- The rescue of the drug to the modern pharmacology clarifies the mechanism of action and explains the adverse effects.
- There are cases of teratogenicity in Brazil due to inadequate use by physicians and/or patients.
- Each case of thalidomide syndrome is a disaster, but we have to take into account the thousands of patients that can be benefited with the correct use of the drug.
In the specific case of ENL we have to emphasize the side effects of steroids (strias, acne, depression, diabetes, hypertension, osteoporosis, cataract) that replace thalidomide.
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