A randomised controlled trial of Azathioprine in leprosy reactions AZALEP.

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Type 1 reactions

- DTH towards *M. leprae* antigens
  - CD4 cells, pro-inflammatory cytokines
  - Prolonged inflammation
- Treated with steroids
  - Little data
    - Cochrane review only 3 trials
    - Response rate range 30-50%
  - Duration and dose of prednisolone
Need for other agents to treat reactions

- Alternatives to prednisolone
  - Improve response rate
  - Avoid adverse effects associated long courses prednisolone
- Azathioprine
  - Acts by inhibiting T cell development
  - Small study in Anandaban Hospital, Nepal (2003). 12 week course improved sensory outcomes
Hypothesis: adding Azathioprine to prednisolone would improve skin and nerve outcomes in T1R.

- Measured by Combined Reaction Score (skin, sensory, motor).
  - Validated by Walker et al. 2010
- Primary outcome: improved combined reaction score outcome.
- Secondary: prevention of recurrence skin and nerve reaction.

4 arm study:
- Prednisolone 20 week plus azathioprine or placebo for 24, 36 and 48 weeks.
Case Definitions
INFIR 2005 study
• Skin reaction
• Motor function
• Sensory function
Patient recruitment:
• Reactional skin lesions
• Acute neuritis
• Impaired sensory
• Impaired motor function
Trial Design

- Ethical Approval: The Leprosy Mission Trust India
- Informed consent
- Sample size: 63 group 25% improvement in Combined Score
- Definitions of worsening
- Criteria for restarting prednisolone.
- Monitoring for adverse effects
  - 2weekly (FBC, LFTs, U&E) until 8 weeks then 4 weekly
Baseline data

- 345 entered trial (86% male) age range 15-60
- MB leprosy (BT 62.3%, BB 5.5%, BL 21.7%, LL 5.8%) 89% borderline leprosy. 62% smear negative
- MDT, (New 40%, on 40%, completed 20%)
Azathioprine Study Flow Chart

345 individuals randomly allocated to treatment

Allocation

Arm 1
Prednisolone (n=87)
Withdrawn due to adverse reaction (n=5)
Defaulted (n=18)
Died (n=0)
Patients completed study (n=64)

Arm 2
Prednisolone with AZA for 24 weeks (n=86)
Withdrawn due to adverse reaction (n=22)
Defaulted (n=19)
Died (n=2)
Patients completed study (n=43)

Arm 3
Prednisolone with AZA for 36 weeks (n=88)
Withdrawn due to adverse reaction (n=18)
Defaulted (n=23)
Died (n=1)
Patients completed study (n=46)

Arm 4
Prednisolone with AZA for 48 weeks (n=84)
Withdrawn due to adverse reaction (n=14)
Defaulted (n=22)
Died (n=1)
Patients completed study (n=47)

Patients excluded from analysis because they received extra steroids (n=66)

Arm 1 (n=18)
Arm 2 (n=21)
Arm 3 (n=15)
Arm 4 (n=12)

Analysis (n=134)

Arm 1 Analyzed (n=46)
Arm 2 Analyzed (n=22)
Arm 3 Analyzed (n=31)
Arm 4 Analyzed (n=35)
Adverse events

- 40% had an infection, 29% gastric pain, 14.5% weight gain.
- 59 adverse events (steroid a/e, gastritis, skin, anaemia)
- High rate of steroid associated a/e
- Patients taking Aza and dapsone developed anaemia
- 4 died, all taking MDT, steroids and aza, fever & diarrhoea, CVA, PUO, pancytopenia, probable MI and sepsis.
- Problematic investigating these patients. No blood cultures,
- Dr Joydeepa Darlong discussing adverse events more.
Outcomes

Modified Intention to Treat Analysis (N= 279)

All patients (n=345) excluding those who received a second course of prednisolone (n=66)

– Last assessment as end point for non-completers
– Combined score difference
– Skin
– Sensory
– Motor
– Maximum possible improvement score 30
3 patients worse and 65 patients no change (0, 0.5, and 1). 16 patients major improvement. The median change in patients in arms 1, 2 and 3 was 3.0, and 4.0 for patients in arm 4 with score difference 10 and more. The baseline and endpoint score differences for patients in each arm were highly significantly (p<0.001). Treatment with azathioprine did not improve outcomes.
Skin Score differences (Baseline to Endpoint) for all patients (n=180) with skin lesions.

Patients: None deteriorated, 38 no change, 57 major improvement

Median score changes for patients in arms 1, 2 and 4 was 3.0, and arm 3 was 4.0, with score differences of 5 and more. The baseline and endpoint score differences for patients in arm 1, 3 and 4 were highly significant (p<0.001), indicating that treatment in these arms produced improvement.
Sensory Score differences (Baseline to Endpoint) for patients (n=104) with Sensory impairment

Patients: None worsened, 66.3% unchanged and 6.7% major improvement. Median score change for patients in arm 1 and 2 was 0.5, and in arm 3 and 4 was 1.0. Score differences significant for patients receiving 48 weeks azathioprine (p=0.0002) and almost significant for patients in arms 1 and 3 (P values 0.0505 and 0.0512 respectively). This suggests that azathioprine might have a beneficial effect on sensory function.
Motor Score differences (Baseline to Endpoint) for all patients (n=184) with Motor impairment

Patients: 3 worsened, 72 no change, 13.1%) major improvement

Median change for patients in arms 1 and 2 was 2.0 and arm 3 and 4 was 1.0. Patients treated with prednisolone only and prednisolone plus 24 weeks of azathioprine had significant improvements in their score differences (p 0.0002 and p 0.0001), no benefit was seen for treatment with 36 or 48 weeks of azathioprine with respect to motor function.
• Significant improvements found from baseline to end of treatment
• Attributable mainly to skin lesion improvement
• Azathioprine does not add to the benefit from prednisolone treatment - combined or skin outcomes
• Azathioprine (48 weeks) gave some improvement in the sensory scores
• Azathioprine (24 weeks) gave significant improvements to motor scores
• Small benefits
Recurrences

Kaplan-Meier curve of time to next course of prednisolone. 48 week group slowest rate of recurrences and least extra prednisolone. Groups not statistically different. Azathioprine did not reduce recurrences.

38% patients on aza needed a further course of prednisolone vs 33% on prednisolone.
Conclusions AZALEP

• First large RCT on a new treatment for T1R and neuritis using a validated scale for measuring outcomes
• Azathioprine does not add to the benefit from prednisolone treatment - combined or skin outcomes
• No significant effect on recurrences
• **Azathioprine not recommended as additional treatment for T1R**

• Basic science to identify key pathways of inflammation.
  – Orlova (2013) identified gene set associated with patients who have T1R: Pro-inflammatory response, arachidonic acid pathway, genes involved in down regulation inflammatory response
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