Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia, risk and benefits up to 9 years of treatment

MSH Follow-up Study. JAMA 2003;289:1645-51 (April 2)

Study Type: POEM

Purpose: SCA patients in the original MSH study (N Engl J Med 1995;332:1317-22, May 18) were allowed to continue, stop or begin hydroxyurea to assess mortality.

Study Duration: up to 9 year follow-up; n = 233 of the 299 (all 66 patients not analyzed were accounted for)

Trial Design: follow-up observational study to a RCT, double-blinded study, multicenter (21 centers, USA and Canada); The original MSH study was designed to test whether hydroxyurea could reduce the number of vaso-occlusive events in adults with SCA. This trial was not designed to detect specific differences in mortality, this is why it is observational.

Patients: not mentioned in this trial

Inclusion: history of more than 3 painful episodes in past 12 months; Hb and retic counts in the range that would not contraindicate hydroxyurea

Exclusion: Not mentioned in this article.

Primary Outcome Events: the number of strokes, renal failure, hepatic failure, cancer, sepsis, fatal events (were assessed by medical records, autopsy)

1. Are the results valid?
   * The follow-up study was not a RCT.
   * observational study that becomes associational data at best

2. What were the results?

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Original MSH trial</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hydroxyurea</td>
<td>placebo</td>
</tr>
<tr>
<td>Death</td>
<td>36 (23.7%)</td>
<td>39 (26.5%)</td>
</tr>
</tbody>
</table>

Causes of death (in order of cause): pulmonary was the main cause; death during crisis; sepsis/infection; cardiovascular disease; CV disease; hepatic dz; GI disease; renal dz; injury/homicide; undetermined

Fetal Hb
- < 5 g/L 36%
- > 5 g/L 15%
p-value .03

Mortality
- 37%
- 18%
p-value .001
(treatment especially beneficial when retic count is <250,000 mm3 and Hb < 9, verses > 9)

Acute Chest
- ≥ 1
- none
p-value

Mortality
- 32%
- 18%
p-value .02

per 3 month hydroxyurea usage
- 5.8%
p-value .04

3. Will the results help me?
   * neutropenia counts did not predict death from hydroxyurea
   * the number of painful episodes did not predict death
   * 3 patients developed cancer
   * 14 had a stroke; 28 with renal failure; 13 with hepatic failure; 3 with malignancy; 38 with sepsis/infection
   * Limitations:
     - no longer randomized
     - selection bias
     - randomized based on painful episodes, a predictor of mortality

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