Issues in Systematic Review of Orphan Drugs: A Case Study of Eculizumab for AHUS

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OBJECTIVES

Atypical haemolytic uraemic syndrome (aHUS) is a rare disease affecting approximately 170 people in the UK. The outcome is often poor, with 53% of familial cases and 37% of sporadic cases resulting in end stage renal failure or death. A systematic review was undertaken to assess the efficacy and safety of eculizumab for aHUS. We report key outcomes and highlight issues of applying standard systematic review methods where the evidence base is not well developed.

METHODOLOGY

1. Electronic searches
We searched 13 databases for relevant studies including MEDLINE, Embase and The Cochrane Library, using the following search strategy: Ovid MEDLINE <1946 to March Week 3 2012>

1 atypical h?emolytic ur?emic syndrome$.tw.
2 ahus.tw.
3 1 or 2

2. Study selection
We independently reviewed citations and evaluated full publications of all potentially eligible studies. Studies meeting the following criteria were included: i. Patients with aHUS, ii. Receiving eculizumab, iii. All study designs included, except case histories.

3. Data extraction
Data were independently abstracted from studies by two investigators. The prospective studies identified by the systematic searches were appraised using an adapted checklist criteria[1] for non-randomised studies.

RESULTS

1. Search results

- Three eculizumab studies were identified from the search (Fig. 1).
- Two single arm international multisite prospective studies (C08-002 & C08-003) & one single arm retrospective study (C09-001R) were included in the review.
- No randomised or controlled studies were identified.
- Additional efficacy & safety data were obtained from US FDA website.

RESULTS CONTINUED

2. Efficacy results:

Normalisation of platelet count - In Study C08-002, 14/17 patients (82%) achieved a normal platelet count. In study C08- 003, platelet count normalisation occurred in 18/20 (90%) of patients.

- **Thrombotic microangiopathy activity (TMA)** - In study C08-002, 15/17 patients (88%) achieved TMA event free status, whilst in Study C08-003, 80% of patients achieved TMA event free status.
- **Estimated Glomerular Filtration Rate (improvement) –** Improvement in eGFR was observed in 9/17 patients (53%) in study C08-002. In study C08-003, 1/20 (5%) patients showed improvement in eGFR.
- **Adverse events** - Were frequent with hypertension and upper respiratory tract infection affecting about a third of patients in the prospective studies, although these may be complications of aHUS.
- **Death** - No deaths were reported in the two prospective studies at a median follow-up period of 64 weeks.

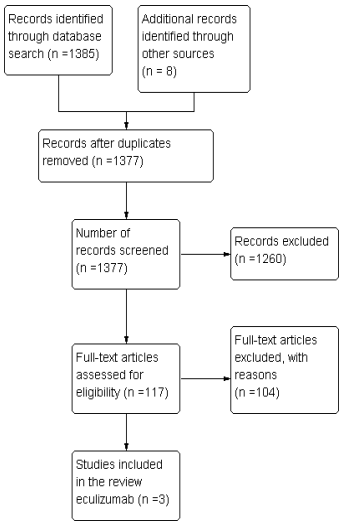

Figure 1. Search results

3. Quality assessment results
Selection and eligibility criteria were not clearly reported in the two prospective studies and it is unclear if the participants enrolled are representative of normal clinical practice. It was not clear from the study descriptions if patients were recruited prospectively. None of the participants were recruited consecutively.

ISSUES WITH UNCONTROLLED ORPHAN DRUG STUDIES

- Due to absence of a control group, inference of treatment effects may be confounded, and it remains uncertain in this study whether all patients responded to eculizumab or even required treatment, as reports indicate that some patients with aHUS experience natural recovery without any therapy[2].
- Randomising patients with rare diseases may be impractical unless international registries are kept to enable sufficient identification of patients for recruitment. Where the risk of death is high, ethical concerns may prevent the use of RCTs, or patient withdrawal studies. Therefore transparent reporting of patient recruitment and selection is essential to limit selection biases when evaluating uncontrolled studies.
- Study data were scarce and derived from abstracts. Additional information were obtained from the US Food and Drug Administration and the European Medicines Agency websites. Complete reporting is needed in orphan diseases to facilitate the evaluation of the clinical and cost effectiveness of treatment and provide clinicians & policy-makers with sufficient evidence to make informed decisions.
- Adverse events were frequent but without a control arm it remains unclear if these are treatment related or complications of aHUS. Establishing global patient registries would provide insights into the natural history of this rare disease.
- Long-term follow-up data are needed for all outcomes and where surrogate outcomes are used, these should be validated to demonstrate the relationship between surrogate and patient-related outcome[3].

CONCLUSIONS

The issues highlighted here are of concern in the review of other rare diseases, where information may also be scarce. Guidance is needed on appropriate study designs. There is a need for validated surrogate outcomes and final patient related outcomes, a need for registries of baseline data, long term follow-up data and adverse event information to enable the monitoring of the natural course of the disease. Guidance is needed on best practice for the recruitment and selection of patients for trials of treatments for rare diseases.

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