Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura

CRD summary
The review summarised the efficacy and safety of rituximab for the treatment of adult patients with idiopathic thrombocytopenic purpura (ITP). The authors concluded that providers should avoid indiscriminate use of rituximab for ITP and that randomised controlled trials are urgently needed. The conclusions were derived from a very weak evidence base and the need for more substantial research is justified.

Authors' objectives
To review the literature on the efficacy and safety of rituximab for the treatment of adult patients with idiopathic thrombocytopenic purpura (ITP).

Searching
MEDLINE (from 1966), EMBASE (from 1980) and the Cochrane Controlled Trials Register were searched up to April 2006. In addition, electronic databases of the American Society of Hematology and American Society of Clinical Oncology were searched (1997 to 2005), bibliographies of relevant articles and reviews were checked, and authors were contacted for additional citations. The search terms were reported and no language restrictions were applied.

Study selection
Study designs of evaluations included in the review
All study designs were eligible for inclusion. The studies had to enrol five or more patients if they did not contain information on safety.

Specific interventions included in the review
Studies on rituximab were eligible for inclusion in the review, whereas studies investigating re-treatment with rituximab were excluded. In the included studies, rituximab was administered mainly as a weekly infusion of 375 mg/m2 for 4 consecutive weeks.

Participants included in the review
Studies of patients with ITP who were older than 16 years of age were eligible for inclusion. Criteria for exclusion were: secondary causes of thrombocytopenia such as splenomegaly, hepatitis B or C virus infection, human immunodeficiency virus infection, lupus, antiphospholipid antibody syndrome, bone marrow failure syndromes, drug-induced thrombocytopenia; malignancy such as chronic lymphocytic leukaemia and lymphoma; or the Evan syndrome. The patients in the included studies had ITP for a median duration of 21 to 134 months, where reported, and their age ranged from 16 to 89 years. Most patients had received corticosteroids and over half had had splenectomy; some patients had previously received treatment with immunosuppressants.

Outcomes assessed in the review
Criteria for the outcomes were not specified. For the included studies, platelets counts, number of patients with complete (more than 150 platelets per 1E9 cells/L), partial (50 to 150 platelets) or overall (more than 50) platelet count responses, time to response, response duration and toxicities were extracted.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the studies. Any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers (haematologists with expertise in research methods) independently and blind to the author, journal, publication data and main results, assessed the following features: prospective data collection, consecutive patient enrolment, clearly stated duration of follow-up and description of losses to follow-up. Any disagreements were resolved by referral to independent adjudication.

Data extraction
Two reviewers extracted the data: proportion of patients with complete, partial or minimal platelet count responses together with the authors' definitions; duration of platelet count response; patient characteristics before the intervention and results; study design and use of controls, and sources of funding. Individual patient data were used where available.

Methods of synthesis
How were the studies combined?
The studies were combined using a random-effects model to estimate the weighted mean proportion of the different responses together with their 95% confidence intervals (CIs). Continuous variables were summarised with medians, minimum and maximum values, and interquartile ranges (while assuming a normal distribution). The toxicities were grouped as mild or moderate (grade 1 and 2 of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3), severe or life-threatening events (grade 3 to 4) and events of death (grade 5).

How were differences between studies investigated?
Some differences between the studies were discussed in the text.

Results of the review
Thirty-one studies (n=335) met the inclusion criteria, of which 19 provided effectiveness data (n=313): 18 single-arm cohort studies (n=290) and 1 dose-finding phase II study (n=23). Seven studies were prospective, 7 studies were retrospective, and for 5 studies this design feature was unclear. Twenty-nine studies reported safety data.

None of the studies included a control group. One study described the enrolment of consecutive patients, 11 studies stated the duration of follow-up and 3 studies reported losses to follow-up.

The weighted means for complete response after treatment with rituximab were 46.3% (95% CI: 29.5, 57.7; based on 13 studies). A partial response was observed in 24% (95% CI: 15.2, 32.7; 16 studies), an overall response (more than 50 platelets) was reported for 62.5% (95% CI: 52.6, 72.5; 19 studies).

The median time to response was 5.5 weeks (interquartile range: 3.0, 6.6; 6 studies) from the first dose of rituximab. The median response duration was 10.5 months (interquartile range: 6.3, 17.8; 16 studies).

Sixty-six patients (22%) in 29 studies showed a mild to moderate adverse event, in the majority infusional reactions. Ten patients (4%) experienced severe or life-threatening events and 9 patients (3%) died.

Authors' conclusions
According to the data, providers should avoid indiscriminate use of rituximab for ITP. Randomised controlled trials (RCTs) are urgently needed.

CRD commentary
The review addressed a clear question and some inclusion criteria were clearly defined. The search for published studies was limited but included efforts to locate unpublished studies, thus helping to reduce publication bias. In addition, studies published in any language were eligible, which helps avoid the introduction of language bias into the review. The reviewers took measures throughout the review process to reduce errors and bias. The included studies represented a very limited evidence base, with poor designs and extremely small samples. It was not entirely clear for
all variables how the various pooled estimates were derived. The quality of the included studies was assessed and taken into account. The conclusions regarding effectiveness and safety were derived from a very weak evidence base and the need for more substantial research is justified.

Implications of the review for practice and research
Practice: The authors stated that until RCTs are available, they would caution against the indiscriminate use of rituximab for the treatment of ITP.

Research: The authors stated that there is an urgent need for RCTs of rituximab in ITP. Furthermore, the optimal timing, dose and schedule of rituximab in ITP is still uncertain. RCTs can resolve the question of whether a favourable response following early administration of rituximab simply reflects spontaneous platelet count recovery.

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