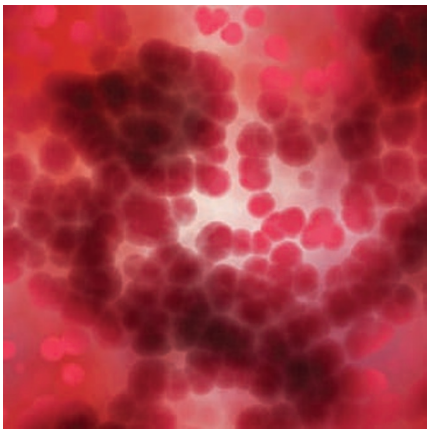
CHRONIC KIDNEY DISEASE

New hope for patients with pure red-cell aplasia or hypoplasia

In rare cases, treatment of patients who have chronic kidney disease (CKD) with recombinant erythropoietin leads to the production of neutralizing anti-erythropoietin antibodies, which can cause pure red-cell aplasia or hypoplasia. "These are devastating, life-threatening conditions," states Iain Macdougall of King's College Hospital, London, "for which virtually no treatment exists". Macdougall and colleagues say that they have achieved encouraging results treating patients with CKD and red-cell aplasia or hypoplasia with a synthetic erythropoietin-receptor agonist.

Anemia is a common complication in patients with CKD, particularly in those undergoing dialysis. Recombinant erythropoietin preparations, such as epoetin α, are therefore routinely administered to patients on dialysis to increase the production of red blood cells. A very small number of these patients, however, develop antibodies that cross-react with native erythropoietin. This immune response leads to a decrease—or even a complete shut-down—of erythropoiesis. This is a potentially deadly condition for which the only current treatment, administration of immunosuppressants, has limited efficacy because re-exposure to recombinant erythropoietin can reinduce the deleterious immune response. Macdougall *et al.* conducted an open-label, single-group study of 14 patients with CKD who had acquired erythropoietin-antibody-based red-cell aplasia or hypoplasia following treatment with epoetin α, epoetin β or darbepoetin α. The investigators treated these patients with Hematide® (Affymax Inc., Palo Alto, CA, USA), an investigational synthetic peptide-based erythropoietin-receptor agonist with an amino acid sequence unrelated to either native or recombinant erythropoietin. Phase I and phase II trials run by Affymax, the sponsor of Macdougall *et al.*'s trial, indicate that Hematide® can stimulate erythropoiesis in healthy volunteers and in patients with CKD or cancer.

Participants in the study reported by Macdougall *et al.* were administered an initial dose of 0.05–0.075 mg/kg body weight of Hematide® every 4 weeks for a median of 28 weeks. At the end of treatment, the median hemoglobin concentration increased from 90 g/l at baseline (a level achieved with support from blood transfusions) to 114 g/l,



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and the median peak counts of reticulocytes increased from 10^{10} per liter to $>10^{11}$ per liter. Most importantly, 13 of 14 participants no longer required regular blood transfusions.

In Macdougall's opinion, these results demonstrate the trial's success. Anne-Marie Duliege, study co-author and Affymax Chief Medical Officer, states that "Affymax is fully committed to developing Hematide® for the management of anemia in patients with CKD", and that "this drug is being investigated in phase III trials, the results of which will be available in 2010."

Baldo Lucchese

Original article Macdougall, I. C. *et al.* A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. *N. Engl. J. Med.* **361**, 1848–1855 (2009)