TOO MUCH OF A GOOD THING

Doctors in the US use epoetins more aggressively than those in the UK. **Alison Tonks** reveals how recent research has raised questions about US guidelines

Erythropoietin is a glycoprotein hormone with a long and controversial history. Thousands of patients worldwide rely on synthetic erythropoietins such as epoetin alfa to alleviate the anaemia that accompanies chronic renal disease and chemotherapy for cancer. But despite decades of use, experts can't seem to agree on one fundamental aspect of treatment: how aggressively should doctors use these agents to drive patients' concentrations of haemoglobin back towards normal?

Getting the answer should be a relatively simple matter—a few decent trials comparing the various options, usually full or partial correction of anaemia. But in the case of epoetin the truth has been lost in a blizzard of professional polemic complicated by the vested interests of big business. Balance is critical. Too little treatment and patients with chronic kidney disease are condemned to a lifetime of exhaustion, misery, and blood transfusions. Too much and they could be threatened with an increased risk of death.¹ Add to this the fact that synthetic erythropoietin is a lucrative best seller for a company with a virtual monopoly in the US, and a fairly straightforward clinical issue becomes a whole lot more complicated. Overtreatment is emerging as a real problem, particularly for US patients on haemodialysis. Over half have haemoglobin concentrations above those recommended by the Food and Drugs Administration, according to one leading commentator.²

The simmering controversy about the best haemoglobin concentration for patients with chronic kidney disease eventually boiled over in November last year when the *New*

England Journal of Medicine published two trials showing that aiming too high was at best an expensive waste of time and, at worst, dangerous.^{3 4} Both trials enrolled patients with chronic kidney disease who did not yet need dialysis or transplantation. In the largest, treatment with epoetin alfa to a target haemoglobin concentration of 135 g/l was associated with a significantly higher risk of death, heart attack, stroke, or heart failure than a lower target of 113 g/l.³ The results were so conclusive, the trial was stopped early. In a second smaller trial, full correction of anaemia with epoetin beta (target 130-150 g/l) failed to improve cardiovascular outcomes as expected and was associated with a faster decline in renal function.⁴

A hard hitting commentary by one of the journal's national correspondents Robert Steinbrook, declared that overtreatment with synthetic erythropoietins was unsafe, widespread in the US, and possibly driven by the drugs industry's influence over national guidelines. It also questioned whether guidelines issued by the National Kidney Foundation may have been tainted by multimillion dollar contributions from the pharmaceutical industry.² The commentary was not published. The journal ran a less critical editorial, which was cowritten by Julie Ingelfinger, one of the *New England* journal's deputy editors, and Guiseppe Remuzzi, a nephrologist.⁵ Further controversy arose when the *Wall Street Journal* claimed that Dr Ingelfinger was the immediate past president of the National Kidney Foundation's Massachusetts chapter—a point she did not declare in her article.⁶

A spokeswoman for the *NEJM* said: "We

have a long-standing policy at *NEJM* not to discuss articles that we have not published. Similarly, we cannot acknowledge whether we considered an article." She also added: "The Ingelfinger and Remuzzi editorial was not a replacement for anything. It was assigned at the time that both Original Articles (CREATE and CHOIR) were accepted for publication, as is our standard procedure. Also, it should be noted that Dr. Ingelfinger's National Kidney Foundation involvement was limited to a purely voluntary position with the local affiliate of the NKF, a role that ended before the editorial was assigned. She has no involvement with the national organization, nor was she involved in the conception, development, or writing of anemia guidelines for the NKF or any other body."

Steinbrook's commentary appeared a day later on the *Lancet's* website.² Bits of it also appeared a month later in the *Wall Street*

patients having dialysis in the US now have haemoglobin concentrations higher than the 120 g/l specified by prescribing information and approved by the Food and Drugs Administration.² A fifth have haemoglobin concentrations above 130 g/l.

Perverse incentives within Medicare's reimbursement system for epoetin products may also be contributing to overtreatment. Professor Coyne and others claim that epoetin is profitable for dialysis providers, who are paid more in reimbursements than it costs them to acquire the drugs. The big profit making chains depend on the administration of epoetin for their income, so there is a built in temptation to use more.^{8 10}

Things have been slightly quieter in the UK, where the National Institute for Health and Clinical Excellence (NICE) has been busy preparing and publishing guidance on treating anaemia in patients with chronic kidney disease. In September last year the institute recommended that doctors prescribe synthetic erythropoietins (officially known as erythropoiesis stimulating agents) to adults "likely to benefit in quality of life and physical function," and to maintain stable haemoglobin between 105 and 120 g/l.¹¹ The guidance also recommends reviewing the dose for patients whose haemoglobin concentration goes over 120 g/l. The NICE guidance predates the trials in the New England journal, both of which vindicate the institute's

more cautious approach to treatment.

Two things set NICE apart from guideline developers in the US. Firstly, "NICE is forced to consider the cost effectiveness of treatments as well as their benefits and risks, something it's often criticised for," says Penny Ackland, general practitioner and member of the guideline development group that formulated NICE's recommendations on anaemia in patients with chronic kidney disease. "Synthetic erythropoietins get less cost effective beyond a certain threshold haemoglobin because the dosage required, and therefore the costs, escalate fast whereas the benefits, such as quality of life, don't seem to improve much, if at all." Secondly, NICE is a public

ERYTHROPOIETIN

- Natural erythropoietin is a glycoprotein hormone produced mainly by peritubular cells in the kidney
- It regulates the production of red blood cells by controlling the proliferation and differentiation of erythroid progenitor cells in bone marrow
- Synthetic erythropoietins are made using recombinant DNA technology
- Epoetin alfa and beta both have 165 amino acids in almost identical sequence to those in the natural protein
- Darbepoetin is a derivative of epoetin and has a longer half life

Journal, which told readers that the National Kidney Foundation receives over half its financial support from "corporate and organisational partners" including Amgen, the principle manufacturer of epoetin products for sale in the US. Amgen is also the "founding and principle sponsor" of the foundation's guidelines on anaemia of chronic kidney disease.⁶ The company denies having any influence over the content of the guidelines, and the National Kidney Foundation is also emphatic on this point stating on its website "In every [KDOQI] guideline, a rigorous scientific process has been used that includes independence of work groups, comprised of volunteer nephrologists and other healthcare professionals, and total separation of financing and content. To ensure that sponsors do not influence work group deliberations or guideline content, sponsors have never been informed or involved in any aspect of guide-

line development."⁷ But critics still argue that their close association undermines the guidelines' credibility. Daniel Coyne, a renal specialist from the Washington University School of Medicine recently wrote: "Physicians caring for patients with chronic kidney disease and receiving dialysis should not wait for the NKF opinions, nor necessarily trust or follow them."⁸

The National Kidney Foundation's current guidelines recommend a relatively high target haemoglobin concentration for patients with chronic kidney disease—between 110 and 130 g/l—although a revised update is imminent,⁹ and use of epoetins continues to increase. Steinbrook writes that over half the

body that accepts no sponsorship from industry and has a robust and open policy on competing interests.

Dr Ackland estimates that 85%-95% of dialysis patients in the UK need synthetic erythropoietin and says the potential for overtreatment is an emerging problem that has yet to surface in the UK. "It's possible that the ideal haemoglobin for people with chronic kidney disease is somewhat lower than that which is considered normal for the general population," she says, "We don't know precisely why, but it's beginning to look as though our original intuition 10 years ago to restore haemoglobin concentrations to normal was probably wrong. But it's hard to generalise. What we need is more precise information about whether some groups might benefit from targeting higher levels of haemoglobin, while others would be better with lower targets."

NICE has no plans to revisit its guidance on chronic kidney disease before the usual two year review, but a new technology appraisal considering the use of synthetic erythropoietins for patients having chemotherapy for cancer is due to be published in November. The latest draft warns doctors not to give erythropoietins to patients with anaemia due to chemotherapy outside the confines of a good clinical trial. There's no good evidence that treatment improves patients' quality of life or prolongs survival, and use of these agents is "very unlikely" to be cost effective, the draft says.¹²

Epoetin alfa, epoetin beta, and darbepoetin (a longer acting agent) are all licensed for the treatment of selected cancer patients. They are also recommended by some American and European guidelines, including those published by the European Organisation of Research and Treatment in Cancer. So the institute probably wasn't surprised by an appeal from drug manufacturers Amgen (which markets darbepoetin in the UK), Janssen-Cilag (which markets epoetin alfa), and Roche (which markets epoetin beta). NICE dismissed most of their grounds for appeal in June last year, except for a few details about specific patients groups and cancers. These will be reviewed before the appraisal is finalised.

NICE guidance on epoetin and other erythropoiesis stimulating agents has been largely

ignored in the US. But Robert Steinbrook is one admirer of the NICE approach to "improving the quality of guidelines and minimizing the potential for inappropriate influences."¹³ In his *Lancet* leader he wrote: "Given the billions of dollars at stake for the drug and dialysis industries, [guidance on anaemia] is likely to receive the broadest acceptance if developed without industry support, and by experts without relevant financial associations."² Meanwhile, further evidence has emerged that epoetins can be too much of a good thing. In a recent meta-analysis in the *Lancet*, a target haemoglobin concentration higher than 120 g/l was linked to excess deaths (risk ratio 1.17, 95% confidence interval 1.01 to 1.35), among patients with chronic kidney disease. Patients on haemodialysis had a higher risk of shunt thrombosis (1.34, 1.16 to 1.54).¹

Giovanni Strippoli, a leading researcher on synthetic erythropoietins and editor of the Cochrane renal group said: "There is now a substantial body of evidence showing that in people treated with these agents a target haemoglobin of more than 120 g/l is harmful. There is emerging agreement among scientists and researchers, but important information is not being rapidly disseminated to doctors on the front line. As the *Wall Street Journal* implied, there may be other influences at work here, including marketing. Opinion is shifting, but it may not be shifting fast enough and if we don't change things, patients' lives will be put at risk. In the *Lancet* meta-analysis, there were about 12 extra cardiovascular events for every 100 patients treated to a higher target haemoglobin, compared with a lower target. Ongoing trials aiming for higher target haemoglobins should in my view be stopped."

He's particularly concerned about a large ongoing trial known as TREAT (trial to reduce cardiovascular events with Aranesp therapy). In one arm, patients are given darbepoetin to a target haemoglobin concentration of 130 g/l. The control arm has a target of just 90 g/l.¹⁴ "This trial may result in harm to patients, based on what we already know from previous trials, and we ask for public disclosure of the reasons for its continuation. It's time to move on, and we are starting a trial of fixed doses of erythropoietin, not targets. These kinds of trials should at least tell us if it's the drugs themselves or the increase in haemoglobin that's doing the damage."

The US regulators have already taken steps to stop doctors overtreating patients in the US. A strongly worded safety alert updated in March, reminds doctors that the aim of treatment is to help patients avoid red cell transfusions. It says darbepoetin, epoetin alfa, and other erythropoiesis stimulating agents increase the risk of death and serious cardiovascular events when dosed to achieve a target haemoglobin greater than 120 g/l. Doctors should use the lowest possible dose that works, and withhold treatment if a patient's haemoglobin concentration goes above 120 g/l.¹⁵

Alison Tonks is associate editor, BMJ, London
atonks@bmj.com

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