Roxadustat

A promising treatment for anaemia in chronic kidney disease

There is a lack of effective treatment options for managing anaemia in patients with non-dialysis dependent chronic kidney disease (CKD). Dr Robert Provenzano, Wayne State University School of Medicine, Michigan, USA, is exploring one possible drug to tackle this, called Roxadustat. He pooled the results of three clinical trials and concluded that Roxadustat is a promising therapeutic option for treating anaemia in this patient group.

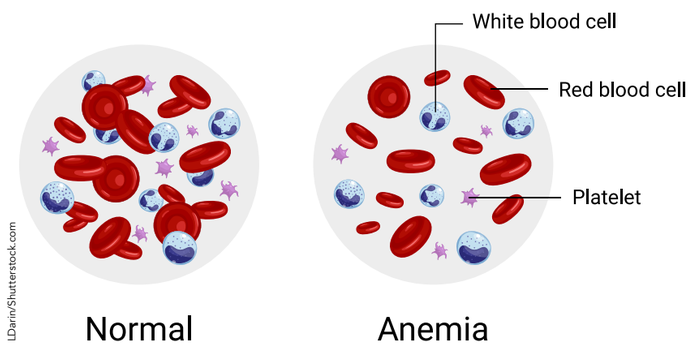
More than one in seven (15%) of people in the US have chronic kidney disease (CKD), making it one of the top causes of death. This equates to around 37 million people who have developed some level of damage to their kidneys, although about 90% of patients will be unaware this has happened.

CKD occurs when the kidneys do not work as effectively as normal. Diabetes and hypertension account for over 75% of CKD, but it is also associated with ageing and can be influenced by other factors, such as genetics, certain medications, and smoking. CKD is a progressive condition; however, there are usually no symptoms of kidney disease until the disease is more advanced. At this stage, individuals may experience tiredness, water retention, changes in urination, itchy skin, or muscle cramps. Since there is no cure for CKD, treatments focus on slowing progression and managing complications associated with poor kidney function.

COMPLICATIONS OF KIDNEY DISEASE

One of the complications associated with the progression of CKD is anaemia. Kidneys produce a hormone called erythropoietin that stimulates the bone marrow to generate red blood cells. When the kidneys aren't working properly, they produce less erythropoietin and, therefore, fewer red blood cells are generated. While there are different forms of anaemia, due to low iron levels or low B vitamin levels, a lack of red blood cells to carry oxygen round the body can also contribute to anaemia. Anaemia is defined as haemoglobin (a protein in red blood cells) levels of less than 12g per decilitre for women and less than 13g for men.

Unfortunately, only a very small number (3%) of patients with CKD-related anaemia receive treatment. Still, data shows that effective treatment of anaemia in this patient group results in improved clinical outcomes and that, left untreated, anaemia can cause higher levels of hospital admissions and mortality. Undertreatment of anaemia has many reasons. Current therapies with erythropoietin require a subcutaneous (under the skin) injection weekly or every other week. Additionally, supplemental iron is often required, and this is typically given intravenously. This schedule puts an enormous burden on patients who need to schedule, travel to, and spend time at multiple appointments. This burden is magnified for those with lower socioeconomic status, who may not have transportation or aren't able to take time off from work. It's therefore not surprising that few receive treatment, and ultimately may need emergency blood transfusions.



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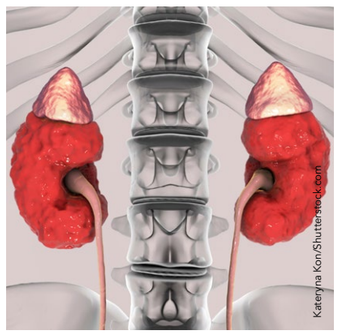
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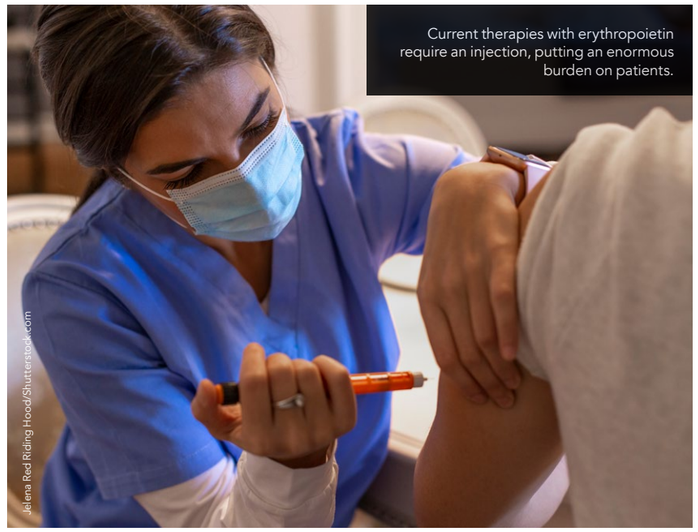
Diseased kidneys with adrenal glands.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Current therapies with erythropoietin require an injection, putting an enormous burden on patients.


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Patients that don't get treated for anaemia may need emergency blood transfusions.

There have also been safety concerns about the use of synthetic erythropoietin, as it was shown to be associated with serious cardiovascular events, such as strokes, when given in high doses or when targeting higher haemoglobin levels. Therefore, there is an urgent need for new, oral, and safe treatments for anaemia, which CKD patients can use at home.

In 1995, scientists discovered a family of proteins which stimulate genes that trigger the natural production of erythropoietin as well as the bone marrow to produce more red blood cells. Increasing red blood cell production in low-oxygen environments (for example, high altitudes) allows the body to use the available oxygen most effectively.

The novel drug, Roxadustat, allows stabilisation of these proteins, resulting in greater production of erythropoietin and red blood cells. It also increases iron availability, which can also be a factor associated with anaemia. The drug can be taken as a pill three times a week, making it very easy for patients to take. Roxadustat is already approved for use in many countries, including the EU, China, and Japan.

CLINICAL TRIALS

Dr Robert Provenzano, Wayne State University School of Medicine, Michigan, pooled together the results of three randomised clinical trials to investigate the efficacy and safety of Roxadustat.

Each of the studies was a Phase 3 trial using a double-blind approach. This means that the aim of the research was to compare a new treatment to an existing one for a specific group of patients. However, neither the participants or the researchers knew whether participants were given Roxadustat or a placebo (in this case, a sugar pill).

The studies varied in duration; two were event driven, meaning that they ran until a defined number of cardiovascular events had been observed, even though

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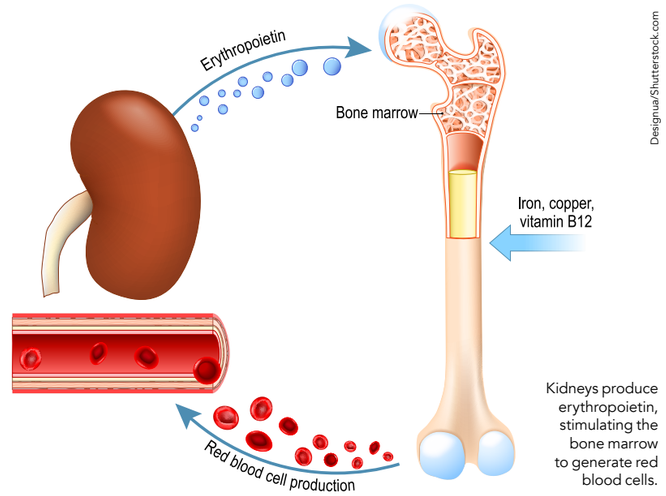

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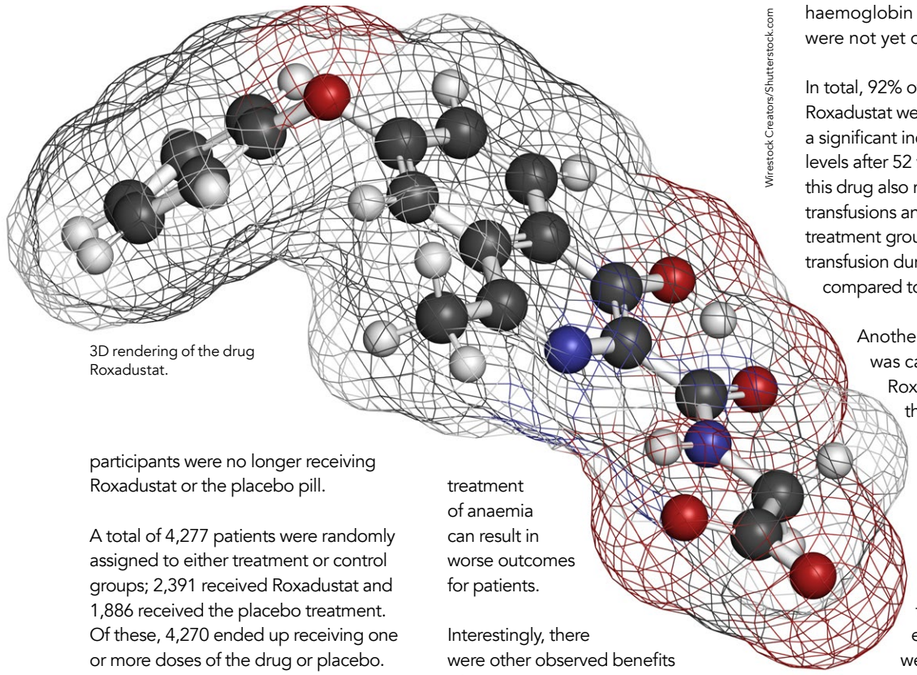
Kidneys produce erythropoietin, stimulating the bone marrow to generate red blood cells.



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3D rendering of the drug Roxadustat.

participants were no longer receiving Roxadustat or the placebo pill.

A total of 4,277 patients were randomly assigned to either treatment or control groups; 2,391 received Roxadustat and 1,886 received the placebo treatment. Of these, 4,270 ended up receiving one or more doses of the drug or placebo. These patients had CKD and anaemia but were not dependent on dialysis. Baseline characteristics were similar between both groups; average haemoglobin levels and kidney function were not significantly different between the groups at the start of the study. Patient demographics were also similar.

The main measurement used in the studies was a change in haemoglobin levels. Secondary measurements included iron levels and the need for alternative treatments to manage anaemia, such as blood transfusion or intravenous iron supplementation.

treatment of anaemia can result in worse outcomes for patients.

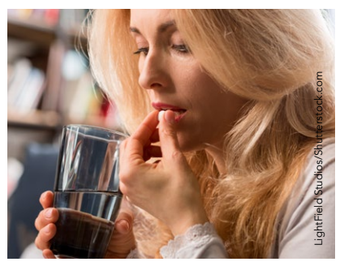
Interestingly, there were other observed benefits of treatment, with one study showing that cholesterol levels decreased during the first eight weeks of treatment with Roxadustat. The researchers hypothesise that this may be due to the drug's off-target actions on other genes involved in the cholesterol pathway.

Provenzano shows that the outcomes of the three individual trials were consistent with the pooled analysis of the total data. Overall, the results showed that Roxadustat was more effective than the placebo at increasing haemoglobin in patients with CKD who were not yet on dialysis.

In total, 92% of patients receiving Roxadustat were considered to have had a significant increase in haemoglobin levels after 52 weeks of treatment. Using this drug also reduced the need for blood transfusions and only 5% of patients in the treatment group needed a red blood cell transfusion during 52 weeks of treatment, compared to 15% of the control group.

Another important measurement was cardiovascular safety of Roxadustat, especially given the issues that developed with earlier treatments for CKD-related anaemia. The studies showed comparable numbers of side effects experienced by the treatment and control groups, meaning that cardiovascular events and mortality were not increased in the treatment group.

The ability to treat CKD-related anaemia with Roxadustat has important implications, meaning effective, safe and easy treatment for patients.



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Roxadustat is a convenient, oral medication.

NEW TREATMENT OPTIONS

The ability to treat CKD-related anaemia with Roxadustat, an oral medication, has important implications for patients. It provides a convenient alternative to the current injections required to administer erythropoietin. The drug is also effective, safe, and well tolerated by patients.

Provenzano highlights that the pooled data from the three studies met US and EU defined end points. This means that Roxadustat would meet the requirements set out by the relevant governing bodies in these countries to be registered as a potential therapeutic agent. Patients treated with the drug had better outcomes, including improved haemoglobin levels, reduced need for red blood cell transfusions, and showed no significant increase in adverse events when compared to placebo treatment. One benefit of decreasing the need for a blood transfusion is the avoidance of complications in the future, as a patient's eligibility for a kidney transplant may be affected by transfusion in some cases.

Findings from all three studies suggest that Roxadustat is a viable option for treating anaemia in non-dialysis-dependent CKD patients.

Behind the Research

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Research Objectives

Dr Provenzano and his team conducted three randomised global clinical trials to examine the efficacy and cardiovascular safety of Roxadustat treatment for patients with CKD-related anaemia.

Detail

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Bio
Robert Provenzano is an associate clinical professor of medicine at Wayne State University School of Medicine. He has served as the Chief of the Division of Nephrology, Hypertension & Transplantation; Director of Nephrology Research; and Director of Acute Dialysis Services at St John Hospital & Medical Center in Detroit, MI, and as the Vice-President of Medical Affairs at DaVita. Dr Provenzano has conducted extensive research and published numerous articles and clinical studies on the management of anaemia.

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Collaborators
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References

Provenzano, R, Szczech, L, Leong, R, et al, (2021) Efficacy and cardiovascular safety of Roxadustat for treatment of anemia in patients with non-dialysis-dependent CKD: pooled results of three randomized clinical trials. *Clinical journal of the American Society of Nephrology : CJASN,* 16(8), 1190–1200. doi.org/10.2215/CJN.16191020

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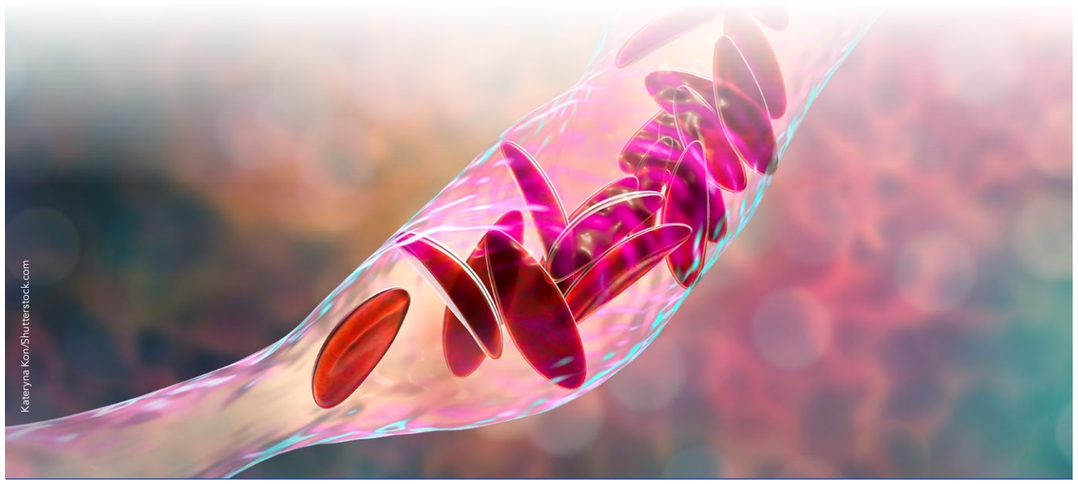
Personal Response

What are the next steps in gaining approval for the use of Roxadustat?

"Roxadustat has been approved in China and Japan for over three years. It has also been approved in the EU member states, Norway, Iceland, South Korea, UK, Netherlands, Chile, and Liechtenstein. In the US, the FDA requested additional dosing and safety trials which are being considered."



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