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A) COMMENTS ON PUBLISHED ARTICLES

There are no differences between non-diabetics and diabetics with respect to the effect of anaemia correction in chronic kidney disease

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Dear Editor,

Although the results from the TREAT[1] study only apply to diabetics, strictly speaking,[2] the comparison between high and low haemoglobin targets affects all types of patients. The meta-analysis by Phrommintikul et al. is currently the most complete overview of the effect of high haemoglobin targets on mortality in chronic kidney disease.[3] With a percentage of diabetics near 40%, the mortality risk ratio with a high haemoglobin target compared with a low target was 1.17 with a 95% confidence interval (CI) between 1.01 and 1.35. When we add the results from the TREAT study, which has a higher overall percentage of diabetics (near 66%) the mortality risk ratio decreases slightly to 1.10 with a 95% CI between 1.00 and 1.21 (Figure 1).

These results contradict the hypothesis that the increase in mortality with high targets is limited to diabetic patients. The only indication for exploring this hypothesis in later studies would have been if the mortality risk ratios for diabetics had been higher than for non-diabetics in the preliminary clinical trials.[3] But nothing in these studies suggests that this is the case.

We must not forget the significance of the meta-analysis results from all of the published controlled randomised studies: the search for high haemoglobins may increase the risk of mortality by a small but important amount (up to 21%), while the probability of high haemoglobins decreasing mortality is practically non-existent. In contrast, the improvement in quality of life generated by high haemoglobin levels is clinically insignificant.[4] Since differences between diabetics and non-diabetics have not been shown, this interpretation should apply to all patients. In absolute terms, diabetic patients will be more vulnerable to the harmful effects of high haemoglobin targets, since they have a higher absolute risk of death, but we must not ignore that non-diabetic patients also have an added risk of mortality.

In the case of stroke, the situation is quite similar: of the three data-bearing studies published prior to TREAT, the stroke risk ratio for a high target was 1.53, with a 95% CI of 0.89 to 2.64. When the TREAT is added, the combined risk ratio becomes 1.81, with a 95% CI of 1.37 to 2.39, without statistical heterogeneity among the studies, that is, without any indication that the TREAT results would be different from the rest (our own calculation). The relative risk of stroke where targets are high is higher than risk of death.

These data do not correspond with the practice of setting higher haemoglobin targets in non-diabetics than in diabetics, as De Francisco et al.[2] propose.

1. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de ZD, Eckardt KU et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361(21):2019-32.
2. De Francisco A, Aljama P, Arias M, Fernández E, Górriz JL, López Gómez JM et al. Corrección de la anemia en pacientes diabéticos con enfermedad renal crónica sin tratamiento sustitutivo: enseñanzas del estudio TREAT. Nefrologia 2010;30(1):15-20.

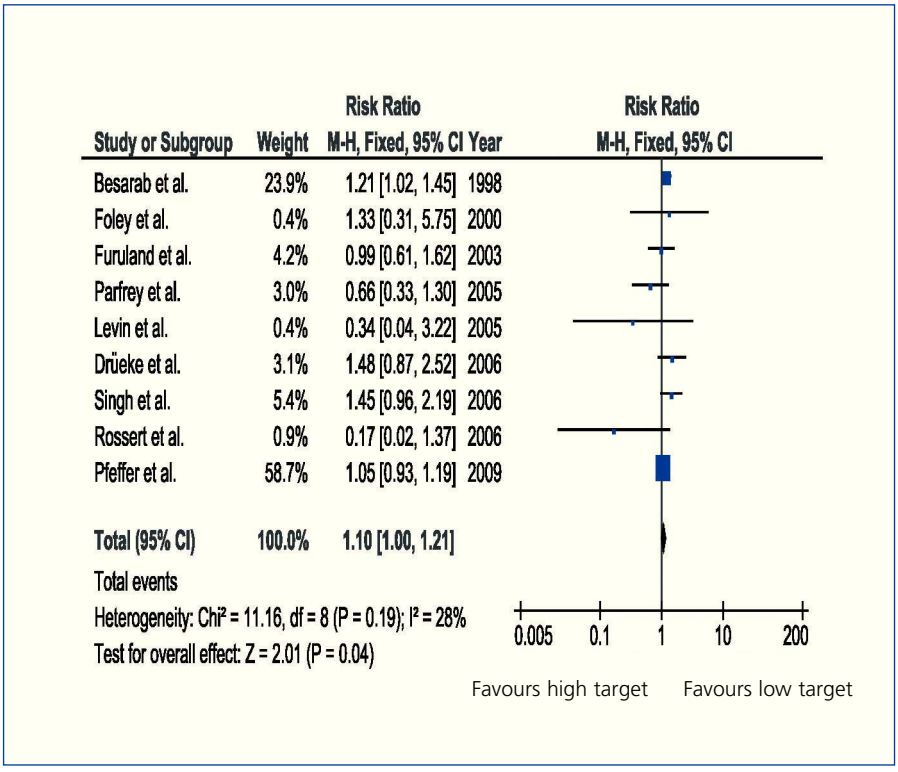

Figure 1. Meta-analyses of the effect of high haemoglobin targets on mortality in chronic kidney disease.

3. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 2007;369(9559):381-8.
4. Clement FM, Klarenbach S, Tonelli M, Johnson JA, Manns BJ. The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. Arch Intern Med 2009;169(12):1104-12.

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Pulmonary toxicity associated with sirolimus following kidney transplantation: computed tomography findings

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Dear Editor,

We read with great interest the letter by Calle et al.[1] describing the case of a patient who underwent a kidney transplant and developed a pneumonitis caused by sirolimus. They related that there are, until now, only seven cases reported of recovery from pneumonitis caused by sirolimus.

We would like to describe the case of a 27-year-old woman with a two-year history of haemodialysis for end-stage renal disease underwent a haplo-identical, living kidney, donor transplantation. Following the procedure, she began immunosuppressive therapy with tacrolymus, mycophenolate mofetil, and steroid. Her renal function was stable and she was discharged with normal serum creatinine levels.

Two months after beginning immunosuppressive therapy she presented with diarrhoea of unknown aetiology. After recovery from the diarrhea, the patient was discharged while using mycophenolate sodium and metronidasol. Six months later, she was admitted with another episode of diarrhea and the tacrolymus was switched to sirolimus.

Ten months after initiation of the sirolimus treatment, the patient was admitted with fever, shortness of breath, and dehydration. Chest X-rays and high-resolution CT of the chest demonstrated bilateral areas of non-homogeneous air space consolidation, mainly in the left upper lobe and lower lobes (figure 1A). Bronchoalveolar lavage revealed hypercellularity with lymphocytosis, and the microbiological evaluation was negative for bacteria, fungi, and viruses. Serological tests for cytomegalovirus were negative. The patient began an empirical, anti-infection treatment with intravenous azithromycin and ciprofloxacin, with no response. The fever persisted with antibiotic treatment and sirolimus was thought to be the cause of the symptoms. When sirolimus was switched to azathioprime symptoms improved within 10 days, and were resolved in 30 days. On the follow-up chest X-ray and high-resolution CT, 30 days after sirolimus discontinuation, the parenchymal abnormalities had improved, with accentuated reduction of the air-space consolidation pattern. There were persisting residual areas of bilateral ground-glass opacities on the high-resolution CT (figure 1B).

Sirolimus (rapamycin) is a potent immunosuppressive drug that has been successfully used in solid organ transplant recipients as an alternative to calcineurin inhibitor therapy.[2-4] The most common side effects associated with this drug are dose-dependent hyperlipidemia, and thrombocytopenia. Unlike calcineurin inhibitors, sirolimus does not induce acute or chronic nephrotoxicity. However, in very rare cases, patients treated with sirolimus may exhibit severe pulmonary toxicity.[2,3]

The symptoms of pulmonary toxicity related to sirolimus are generally non-specific, and may include a dry cough, dyspnea, fatigue, and fever, frequently leading to the initial diagnosis of pulmonary infection.[5] Some reports have described histopathological patterns as a result of sirolimus pulmonary toxicity, but these findings are usually non-specific, consisting of bronchiolitis obliterans with organizing pneumonia,

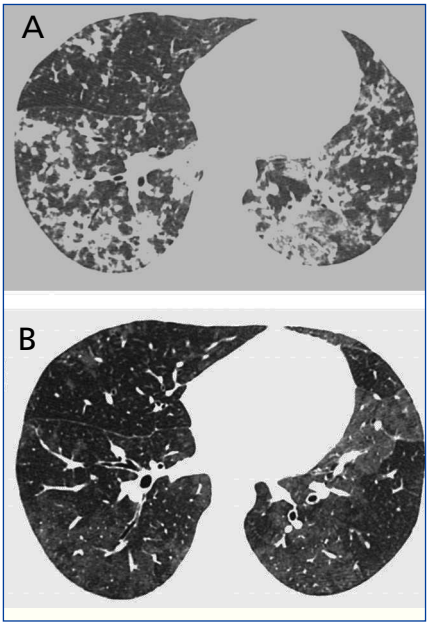

Figure 1. High-resolution CT at the level of the lower lobes (A) (obtained at the time of clinical presentation when respiratory symptoms were evident) demonstrates areas of non-homogeneous air space consolidation in the lower lobes, and mild ground-glass opacities. Follow-up scan (B), taken in the same plain as A, and 30 days after discontinuation of sirolimus, showed a reduction in the air¬space consolidation pattern, with bilateral areas of residual ground-glass attenuation. The expiratory scans did not show air trapping.