Everolimus for renal angiomyolipoma in tuberous sclerosis

In The Lancet, John Bissler and colleagues¹ report the first randomised, double-blind, placebo-controlled, phase 3 trial of everolimus, an inhibitor of mammalian target of rapamycin (mTOR), in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis, and angiomyolipoma. Their findings suggest a clear advantage for everolimus over placebo in reducing angiomyolipoma volume with an acceptable safety profile in patients with tuberous sclerosis.

Tuberous sclerosis is a rare disease affecting one in 5800 livebirths and fewer than one million people worldwide.² However, for these patients it is a severely debilitating disorder, associated with multiple lesions including renal angiomyolipoma, brain subependymal giant-cell astrocytomas (SEGAs), and pulmonary lymphangioleiomyomatosis. The condition is caused by mutations in either TSC1 or TSC2 suppressor genes, resulting in increased mTOR activity. Hence, mTOR inhibitors have a rationale for management, with demonstrated activity in preclinical studies of animal models and patient-derived cell lines.³⁴

Presenting symptoms might be pain, abdominal visceral compression, and bleeding from renal angiomyolipomas (sometimes life-threatening).⁵ As urologists, we believe that size does matter, and since the risk of bleeding seems greater for those angiomyolipomas larger than 3–4 cm,⁶ there is a case for treating larger angiomyolipomas before they bleed. The current standard elective treatments are selective arterial embolisation and surgery (partial or total nephrectomy). Ablative treatments are used in a few cases. Interventions in the emergency or elective settings are complicated by the diminished neurocognitive status of many patients as well as the coalescence of large angiomyolipomas in the kidneys.⁷ Furthermore, our experience of complex angiomyolipomas is that embolisation has nearly a one in two further intervention rate, with only a modest (28%) reduction in tumour bulk.⁸ We thus believe that Bissler and colleagues’ study provides a much-needed beacon of hope for the management of angiomyolipomas associated with tuberous sclerosis.

Other investigators⁹–¹⁰ have previously shown some clinical benefit for another mTOR inhibitor, sirolimus, but more promise is potentially shown in Bissler’s study. Here, 118 adult patients with tuberous sclerosis (n=113) or sporadic lymphangioleiomyomatosis (n=5) and angiomyolipoma of 3 cm or more were randomly assigned in a 2:1 fashion to take daily oral 10 mg everolimus or placebo. The primary outcome was reduction in angiomyolipoma tumour volume of at least 50% relative to baseline at up to 48 weeks, which was achieved in 33 of 79 patients, 42% (95% CI 31–53), of the everolimus group, and none (0–9) of the placebo group. This is a highly statistically significant finding, and, we believe, clinically significant finding, and was independent of sex, age, or race in subgroup analyses.

Everolimus was shown to be safe and adverse events were tolerable, with more stomatitis and acne-like lesions than in the placebo group. This low rate of adverse events led to few drop-outs in the everolimus group (4%). Secondary outcome analyses in this study showed a greater skin lesion response rate for everolimus than placebo, a correlation between plasma VEGF-D and angiomyolipoma volume,¹¹ as well as a novel association with collagen type IV. Finding potential molecular markers would be extremely helpful in this disease to reduce the need for radiological imaging in patients with variable degrees of special needs, who need sedation or anaesthesia for such scans. The authors did not report the SEGAs response rate of everolimus compared with placebo, but will do so once more data are analysed; the paediatric EXIST-1 trial data¹² recently published showed a 35% response rate for everolimus compared with zero for placebo, and it will be interesting to compare these two trials.

The progressive enlargement of angiomyolipomas over time presents clinicians with challenging, indeed limited, opportunity for successful localised intervention. A parasitic-type arterial supply with multiple false aneurysms limits efficacy of embolisation; it seems intuitive that systemic prevention and treatment are awaited and potentially achievable from this study. What is not known, however, is whether previous embolisation or surgical intervention affects response to everolimus, a factor which might influence timing of commencement of the treatment. Another remaining question is how durable this therapy is. During the extension phase of EXIST-1 (median duration 34 months),¹³ the reduction in SEGAs volume was maintained, with no everolimus

Comment
recipient requiring surgery or other therapy for SEGA or hydrocephalus. A similar follow-up analysis will be required for the current study by Bissler and colleagues. The relative costs of a maintenance treatment will also need to be weighed against those of radiological or surgical interventions.

The effect reported for patients with sporadic lymphangioleiomyomatosis is difficult to comment on, since only two such patients received everolimus, one showing a 20% reduction in angiomylipoma volume at 24 weeks and the other a 48% reduction. Since this disease is so rare these data are unlikely to be improved upon, and we have to consider everolimus pragmatically as a potential treatment option for such patients.

We congratulate the authors of this new study, who came together from 24 centres in 11 countries. Their results are promising and are likely to herald a new approach to the treatment of this rare but serious disease.

*Prasanna Sooriakumaran, Christopher J Anderson
Department of Urology, St George’s NHS Trust, London SW17 0QT, UK
sooriakumaran@gmail.com

We declare that we have no conflicts of interest.