Efficacy and Safety of Sirolimus for Renal Angiomyolipoma in Patients with Tuberous Sclerosis Complex or Sporadic Lymphangioleiomyomatosis: A Systematic Review

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Abbreviations and Acronyms

ITT = intent to treat

LD = longest diameter

mTOR = mammalian target of rapamycin

PP = per protocol

RCT = randomized controlled trial

SAE = serious adverse event

sLAM = sporadic lymphangioleiomyomatosis

TSC = tuberous sclerosis complex

Accepted for publication April 29, 2014.

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Purpose: We evaluate the efficacy and safety of sirolimus in the treatment of renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis.

Materials and Methods: A systematic search of MEDLINE®, Embase®, ACP (American College of Physicians) Journal Club, Cochrane CENTRAL (Central Register of Controlled Trials) and Cochrane Database of Systematic Reviews was performed. A secondary hand search was performed in relevant journals, references and the grey literature. The screening, quality assessment and data extraction of the retrieved articles were independently performed by 2 reviewers in duplicate. Studies that reported an angiomyolipoma response or adverse events after the treatment of sirolimus were included in the analysis.

Results: Four prospective nonrandomized studies involving 94 patients were included in the study. The overall response rate of angiomyolipoma was 46.8% (44 of 94) in the first year. In the second year the angiomyolipoma response rate for those patients still being treated with sirolimus was 43.5% (20 of 46) and the response rate of the patients whose sirolimus treatment was discontinued was 5% (2 of 40). The most common sirolimus related adverse reactions were stomatitis, respiratory infection, skin lesions and hyperlipidemia, while serious adverse reactions were rarely observed.

Conclusions: This study shows that renal angiomyolipoma shrank during sirolimus therapy but tended to regrow after the therapy was stopped. In general, sirolimus is an effective and safe therapy for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis.

Key Words: drug-related side effects and adverse reactions, angiomyolipoma, sirolimus, therapeutics

Tuberous sclerosis complex is a systemic autosomal dominant disorder that affects approximately 2 million people worldwide.[1] It is usually caused by decreased or absent expression of *TSC1* (hamartin) or *TSC2* (tuberin) genes. The products (hamartin-tuberin complex) of *TSC1* and *TSC2* are associated with regulation of the mTOR signaling pathway.[2,3] A lack of hamartin-tuberin complex results in the development of tumors in many organs including angiomyolipoma and lymphangioleiomyomatosis.[4]

Lymphangioleiomyomatosis also occurs as a rare sporadic disorder in

0022-5347/14/1925-1424/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.04.096
Vol. 192, 1424-1430, November 2014
Printed in U.S.A.

women without TSC. Approximately 60% of women with sporadic lymphangioleiomyomatosis also have renal angiomyolipoma.[5,6] Angiomyolipoma in patients with sLAM has been shown to be associated with somatic mutation in the *TSC2* gene.[7]

Renal angiomyolipoma is a major clinical feature of TSC and sLAM, which is composed of anomalous vessels, immature smooth muscle tissue and adipocytes. The incidence of renal angiomyolipoma is approximately 80% among patients with TSC. Angiomyolipoma may cause hypertension, renal failure and life threatening hemorrhage. Hemorrhage, which is strongly associated with aneurysm formation, is the major cause of adult deaths from this disease.[8–10] As angiomyolipoma enlarges the size of the aneurysm increases. When the angiomyolipoma or aneurysm is larger than 4 cm and 5 mm, respectively, rupture and hemorrhage will most likely occur.[10]

The main therapeutic options for renal angiomyolipoma are arterial embolization, nephron sparing surgery or nephrectomy if the angiomyolipoma is larger than 4 cm or has caused symptoms.[8] However, these invasive procedures have limits. Angiomyolipoma is usually bilateral, multifocal, larger and difficult to target, especially in patients with TSC, which makes the curability of arterial embolization and success of nephron sparing surgery low. Nephrectomy leads to massive loss of normal renal parenchyma and renal function. Moreover, patients with TSC with angiomyolipoma often require retreatment because of the high incidence of new and recurrent tumors.[6,11,12] Thus, with the limits of these invasive procedures an effective pharmacological therapy is required to address this problem.

Sirolimus, also known as rapamycin, is an immunosuppressive agent that inhibits the mTOR signaling pathway, which has recently been used as a molecularly targeted treatment for angiomyolipoma.[13] In patients with TSC mTOR complex 1 (mTORC1) is over activated due to the loss of hamartin or tuberin protein. This condition causes the phosphorylation of eukaryotic initiation factor 4E binding protein-1 (4E-BP1) and S6 ribosomal protein kinase 1 (S6K1), which leads to dysregulation of cell growth and proliferation.[14–16] Sirolimus can be combined with FK506 binding protein-12 (FKBP-12), forming the sirolimus-FKBP12 complex that inactivates mTORC1, thereby inhibiting the mTOR signaling pathway.[14,17] Based on this mechanism sirolimus is theoretically able to suppress tumor growth in patients with TSC.

Studies have indicated a possible beneficial role of sirolimus in renal angiomyolipoma but the outcomes and adverse events vary.[18–20] The efficacy and safety of sirolimus are still uncertain. In this systematic review we integrate the evidence on the efficacy and safety of sirolimus for renal angiomyolipoma in patients with TSC or sLAM.

MATERIALS AND METHODS

Search Strategy

Literature searches of electronic databases were performed in August 2013. We searched MEDLINE, Embase, the ACP Journal Club, Cochrane CENTRAL and Cochrane Database of Systematic Reviews. Several key terms were used including renal, kidney, angiomyolipoma, sirolimus, rapamycin, tuberous sclerosis and sporadic lymphangioleiomyomatosis. Multiple synonyms of each term were also searched. There were no language restrictions. All retrieved titles and abstracts were screened by 2 reviewers (ZP, LY) independently and in duplicate. Full text publications were reviewed for all potentially eligible studies. The relevant journals, references and grey literature papers were hand searched.

Selection Criteria

All articles identified were screened according to several criteria. The inclusion criteria were human subjects, diagnosis of renal angiomyolipoma, treatment with sirolimus, patients with TSC or sLAM with a followup period of at least 1 year, evaluation of treatment effect on angiomyolipoma or drug adverse reactions. The articles that met the inclusion criteria were included in the analysis. We excluded reviews, editorials, case reports and case series with fewer than 10 patients.

Data Extraction

Data extraction was performed by 2 authors (TW, ZL). We used a predesigned data extraction form to elicit all relevant aspects of the included articles, covering data source, eligibility, methods, participant characteristics, interventions, followup periods, results and limitations of the study. When the trial data were incomplete we contacted the authors for further information. Multiple articles from an identical trial were regarded as a single study.

Quality Assessment

The quality of included studies was assessed by 2 authors (PH, TW) independently. Discrepancies were resolved in consultation with the third reviewer (QW). The nonrandomized studies were assessed with the MINORS (Methodological Index for Non-Randomized Studies). The MINORS included 12 items, the first 8 of which were designed for noncomparative studies. Others were applied to comparative studies. Each item was scored as 0 (nonreported), 1 (inadequately reported) or 2 (adequately reported). The maximum score was 16 for noncomparative studies and 24 for comparative studies.[21]

RESULTS

Results of Systematic Literature Review and Patient Characteristics

We initially identified 640 articles, of which 216 were identified as duplicates. By screening titles