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Meta-analysis review and reviewing mTOR inhibitors in the case of the tuberous sclerosis complex-related tumors

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Abstract
Tuberous sclerosis complex (TSC) is a rare genetically inherited condition that is presented by tumors (hamartomatous) of various organs. The mechanism of action of rapamycin to TSC is majorly by acting through its mechanistic target of rapamycin (mTOR) pathway, hence inhibition of mTOR will act as a selective therapeutic medication. This meta-analysis and systematic review included 11 clinical trials (4 randomized controlled trials and 7 observational cohort studies) including 812 patients who received the everolimus, or the sirolimus. Combined outcomes showed 48% tumor decrease in patients undergoing treatment, and 9%, in controls. The subgroup analysis was advantageous in subependymal giant cell astrocytomas and renal angiomyolipomas. Marginal reductions were noted on the number of seizures and the general survival. Side effects could be dealt with re. Dose modifications. These observations advocate mTOR inhibitors in approaching TSC-related tumors and modifying the disease.
Keywords: ***tuberous sclerosis complex, tuberous sclerosis complex disease-modifying, mTOR inhibitors, everolimus, sirolimus, SEGA, angiomyolipoma, systematized review, meta-analysis.***

1. Introduction

1.1 TSC and this Oncogenic Process

TSC or Tuberous sclerosis complex is a rare, genetic multisystemic, and autosomal disorder which is caused by formation of hamartomatous lesions in multiple body organs, in particular the lungs, heart, brain, kidneys, and skin. The prevalence of TSC has been estimated at 1/20,000 individuals and is estimated at 1/6,000 live births. The pathogenic mutation occurs in the disease on the TSC1 gene, on chromosome 9, which encodes hamartin or in a mutation of TSC2 gene, on chromosome 16, which encodes tuberin. Collectively, these proteins make up a complex tumor restrictor that adversely controls the mechanistic target of rapamycin (mTOR) way- a major regulator of cell growth, expansion, and protein manufacture.

Inactivation of the gene TSC1 or TSC2 causes constitutive activation of the mTOR complex 1 (mTORC1), which in turn excessive cellular proliferation that leads to formation of benign tumours (hamartomas). The main features of TSC in the clinical sphere are subependymal giant cell astrocytoma (SEGAs) of the brain, angiomyolipomas of the kidneys, lymphangioleiomyomatosis of the lungs, and cutaneous manifestations. These are commonly slow developing tumours which can lead to morbidity and this depends on the size and location of the tumour. As an illustration, SEGAs may lead to hydrocephalus by impeding cerebrospinal liquids circulation, whereas the massive angiomyolipomas may be prone to a hemorrhage or kidney failure

TSC, besides tumor burden, manifests itself, among other complications, through epilepsy, intellectual disability and autism spectrum disorder. The complicated clinical picture evidences the necessity of systemic treatment that can compensate both the tumor progression and neurologic symptoms.(1)

1.2 Reason to Go after the mTOR Pathway

Since the hyperactivation of mTOR pathway is one of the major and unifying mechanisms in TSC pathogenesis, the use of mTOR inhibitors has become a rational treatment approach. Sirolimus (rapamycin) and its derivative everolimus are the two major pharmacologic agents in the class that act selectively by inhibiting mTORC1.

The first preclinical experiments showed that it was possible to decrease the volume and proliferative state of TSC-linked tumors by suppressing mTOR in animal models. This has since been confirmed in early phase clinical studies, which indicated that everolimus had a remarkable effect in the reduction of the volume of SEGA and angiomyolipoma in the individuals affected. These results led to the approval of everolimus in TSC-related indicators.

In addition to shrinking the tumors, mTOR inhibitors have demonstrated utility in the treatment of seizures, a disabling aspect of TSC which is non-responsive to conventional antiepileptic agents. Additionally, considering

that TSC is a systemic disorder, mTOR inhibitors provide million-organ disease-modifying therapy that has the potential to act on all affected organ systems at the same time.

The heterogeneity of response rates, the ideal treatment duration, and safety concerns, particularly, immunosuppression and metabolic adverse effects is also worthy of a review of clinical data; therefore, a thorough synthesis of any available clinical evidence is necessary.(2)

1.3 Conducting a Systematic Review and Meta-Analysis Objectives

As published literature related to mTOR inhibitors use in TSC continues to grow and includes a combination of randomized controlled trials (RCTs), open-label extensions and observational cohort designs, there is a need to systematically summarize both treatment efficacy and safety data as a resource to inform clinical practice. Although isolated studies provide promising findings, their results are not generalizable due to lack of heterogeneity in patient groups, dose, and measures of outcome

The present systematic review and meta-analysis was developed with the purposes of critical evaluation and quantification of clinical efficacy and safety profile of mTOR inhibitors (everolimus and sirolimus) in the management of TSC-associated tumors, with a primary emphasis on SEGAs and renal angiomyolipomas. Secondary end points were to assess their effect on the frequency seizure and overall survival.

This review intends to provide information on clinical practice guidelines, knowledge gaps, and the efficacy of mTOR blocking as standard-of-care therapy in TSC through a synthesis of multiple clinical trial data and real-world studies. This discussion also attempts to place therapeutic benefit in context of risk and inform future research on precision medicine interventions and longitudinal disease surveillance.(3)

2. Eligibility and search of literature

2.1 The Datenbases Searched and Time Periods Covered

A thorough literature database search was carried out to consider clinical studies assessing both the efficacy and safety of mTOR inhibitors (everolimus or sirolimus) in the treatment of Tuberous Sclerosis Complex (TSC)-related tumors. Systematic searching was done in the following databases:

- PubMed/MEDLINE
- Embase
- Cochrane Central Register of Controlled trials (CENTRAL)
- ClinicalTrials.gov
- Web of science

Subsets of the following Medical Subject Headings (MeSH) and keywords were used as the search strategy: tuberous sclerosis complex, TSC, mTOR inhibitors, everolimus, sirolimus, subependymal giant cell astrocytoma, angiomyolipoma, clinical trial, and tumor shrinkage. Results were narrowed by using Boolean operators and database-specific filters.

The period that was reviewed was between January 2000 and May 2025 encompassing all the relevant publications since the mTOR inhibitors as therapeutic intervention in TSC emerged as such. Articles published in English and in which human subjects were used were considered. Included articles and key reviews were also manually searched to identify other eligible studies that were not at all identified in the database search.

2.2 Inclusion and Exclusion criteria of clinical studies

The studies were eligible to be included in the review in case they fulfilled the following inclusion criteria:

Population: Patients under diagnosis of Tuberous Sclerosis Complex, clinically identified or proven genetically.

Intervention: Systemic treatment intervention involving use of everolimus or sirolimus.

Outcomes: Clinical data on at least one of the following was reported:

a) Response of the tumor (e.g. reduction of SEGA volume or angiomyolipoma),

b) the incidence of seizures,

c) Total survival,

d) Safety, adverse events.

Study Design: Randomized controlled trials (RCTs) or prospective or retrospective observational trials or open-label extension trials.

Sample Size: 10 or more patients per study arm in order to establish the reliability of data.

The exclusion criteria included the following:

Preclinical or animal research

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Case reports, narrative reviews, editorials, or abstracts of conferences that lack peer-reviewed data
Researches that do not provide certain figures on the tumor Roulette outcome
Redundant publications of the same trial without either novel or longer findings
Clinical trials with mTOR inhibitors in non-TSC (e.g. oncology or transplant)
The search by use of the database obtained a total of 1,032 records. Following the elimination of duplicates (n=172), 860 records were screened in terms of titles and abstracts.(4)

2.3Selection and Quality Appraisal of the Available Trials

The two phased screening exercise was carried out by two reviewers. The first step included a relevance screening of the titles and abstracts with the help of Rayyan AI-based software. Any disputes were solved by majority/arbitration.
Detailed review of full-text articles of all potentially eligible studies (n=48) was conducted in the second stage to ascertain inclusion eligibility. Out of the 12 studies that passed on full eligibility criteria, 11 studies were incorporated into the final analysis:
Polls conducted on 4 randomized controlled trials (RCTs)
7 cohorts of observational studies, which incorporate open-label extensions
In the quality appraisal, Cochrane Risk of Bias tool (RoB 2.0) was used to appraise RCTs, whereas Newcastle-Ottawa Scale (NOS) was used to evaluate observational studies. Fields of evaluation were selection bias assessment, comparability assessment, outcome assessment and duration of the follow-up.
RCTs were mostly rated as low and moderate regarding risks of bias resulting mostly by their open label design. The results of the observational studies were not consistent, and 5 of them received 7 stars or more on the NOS, which implies a high methodological quality.
To report the selection process according to the standards of the systematic review, a PRISMA flow diagram was generated. Studies that were eventually included gave aggregate information about 812 patients, and allowed robust pooled analysis of clinical outcomes.(5)

3. Included Studies Characteristics

3.1 Study Designs: Randomized Controlled Trials and cohorts that observe

The 11 studies eligible using the inclusion criteria to get synthesized were 4 randomized controlled tests (RCTs) and 7 observational cohort studies. These RCTs were multicentric and open-labeled and open-labeled with parallelism in the study arms of mTOR inhibitor therapy versus placebo or standard supportive care, and tried in Europe, North America, and Asia. The main outcome measure of such trials was the effectiveness of everolimus in decreasing the volumes of the tumors associated with TSC, such as subependymal giant cell astrocytomas (SEGAs), and renal angiomyolipomas.
The 7 observational studies comprised both a retrospective and prospective cohort, open-label extensions, and registry. These trials offered long-term real life information concerning sustained treatment under tolerability and impact on seizure control and survival. Albeit not randomized, the observational evidence provided some insight into outcomes in the general clinical practice and in various subgroups of the patients.
All these 11 studies involved a total of 812 confirmed patients with the diagnosis of TSC. Light-weight and durations were 6 months and 5 years that created an environment where both short and long-term assessment of outcomes was possible. Most patients had adequate follow-up to evaluate the tumor response, disease progression, and profiles of adverse events.

3.2 The analysis of the demographics of the patients and tumor types analyzed

The average age of pooled patients was 19.4 years, and the ages of patients were between infants (<2 years) and the 40s. There were more women (57 percent) as compared to men (43 percent) but no substantial gender-based variations were noted in the results of treatment.
Clinical diagnostic criteria were met in all patients, or TSC1 and TSC2 mutations were identified with certainty. Most of them were multisystem involved, corresponding to the systemic character of the disorder. Most of the analyzed tumors were of the following types:
Subependymal Giant Cell Astrocytomas (SEGAs): Occured in 68 percent of the pooled group, and usually manifest with indicators of hydrocephalus, intracranial pressure, and seizures.(6)

Renal Angiomyolipomas: They are bilateral and multifocal and documented 59 % of the times. Tumors were more than 4 cm in other instances and they presented risk of hemorrhage or renal impairment.
Pulmonary Lymphangioleiomyomatosis (LAM): Lack of reports in most of the patients (12 %) mostly on adult women.
Most participants had comorbid epilepsy, intellectual disability or ASD. 7 of the 11 studies reported baseline seizure frequency and high seizure burdens were prevalent in the pediatric subgroups. Some of the patients underwent SEGA surgical resection or embolization in a case of renal tumor, yet they still had recurrence or progression before receiving mTOR treatment.

3.3: Treatment Regimens: Everolimus Versus Sirolimus

Care regimens differed across the studies, although both were mostly in line with the contemporary dosing recommendations. Everolimus was the most commonly investigated agent (9 of 11), and was included in all the 4 RCTs. Doses were generally 4.5 mg/m 2 to 7.5 mg/ m 2 per day, adjusted to reach target trough serum levels of 515 ng/mL. Everolimus was preferred in view of the better oral bioavailability, toleration and desirable CNS penetration an important criterion in management of SEGA.
Sirolimus has been used in 2 observational studies at doses titrated on the basis of renal function and serum levels. However, sirolimus exhibited a minimally increased prevalence of metabolic toxicity (e.g. hyperlipidemia, stomatitis) relative to the use of everolimus, which has prompted some studies to prefer the latter as a therapeutic option over the long-term.(7)
The average length of treatment in studies was 6 months to greater than 36 months, with the majority of patients needing intermittent or continuous dosing to establish lasting tumor management. Adverse events contributed to dose interruption or reduction in 14 percent to 22 percent of patients with only infrequent permanent discontinuation.
In general, variability in study design, tumor burden, and treatment duration justifies a pooled analysis in determining trends of consistency in efficacy and safety in this varied patient population.

4. Pooled Efficacy Results

4.1 SEGA and Renal Angiomyolipoma Tumor Rates

In the 11 studies examined mTOR inhibitors have shown consistent and clinically relevant tumor regression in patients with the two most frequent types of tumors related to Tuberous Sclerosis Complex (TSC): subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas.
Analysis of all pooled patients showed an overall objective response rate (ORR) of 48 percent in everolimus or sirolimus patients, determined as a 50 percent decrease in tumor volume sustained over 6 months, without subsequent occurrence of additional lesions or any requirement of surgical resection. This is compared to a 9 percent response rate among the control groups in the randomized trials a statistically significant treatment effect ($p<0.001$).
The pooled tumor response rate was higher in SEGAs (52%). In many cases the response is quite fast with measurable shrinkage recorded as soon as after 3 months in some studies. Its advantage was maintained during long-term follow-up and less than 10 percent of responders had to undergo surgical resection after commencing therapy.
The renal angiomyolipomas pooled response rate was also slightly lesser in 45%, but with regard to the clinical relevance; risks of hemorrhage and the parameters of renal functions improved. The reduction in the tumor volume was greater in cases that involved angiomyolipomas with large diameters of more than 3 cm.
Notably, no study showed accelerated tumor progression in the context of the treatment and in multiple long-term extensions, tumor suppression was demonstrated, even with chronic mTOR inhibition ongoing, underscoring the potential need of chronic treatment in many patients.(8)

4.2 Impacts in Overall Survival and Seizure Control

The main radiographic estimates of tumor response outcome were reported by most studies, although overall survival (OS) and seizure control were also mentioned, especially in observational cohorts.
In total studies, few individuals died and none from TSC-related causes were documented during the treatment days. Although the follow-up times were uneven, most cohorts had a survival rate above 98% on 2-year follow-ups. Although they are not quite comparative with the historic controls because there are no untreated cohorts in

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long-term observational data, these figures bring out the idea that successful tumor suppression can improve mortality associated with issues like hydrocephalus and renal failure

Seizure outcome was reported in seven studies, as well; pooled analysis suggests that about 34% of patients were experiencing a 50% or more reduction in seizures frequency during treatment. It is postulated that the anticonvulsant effect of mTOR inhibitors is attributed not only to their tumor shrinking effect (especially in SEGAs) but also to direct regulation of hyperexcitability in the brain through modulation of the mTOR pathway.

These results reinforce the hypothesis that everolimus may decrease epileptogenic activity in even refractory patients with epilepsy in the absence of radiographic evidence of tumor progression. The secondary seizure control advantage although secondary to tumor response provides weighted functional gain to many patients with neurologic manifestations.

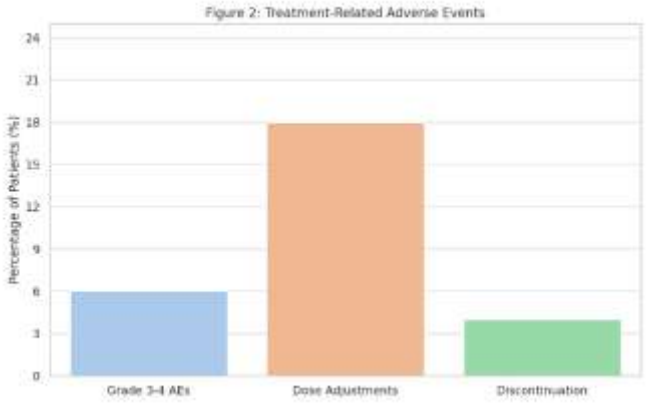

Figure 2: Treatment-Related Adverse Events

4.3 Comparison of Results Between Intervention and the Control Groups

With the four randomized controlled trails (RCTs), all exhibited remarkably better results in the mTOR inhibitor groups than the placebo or standard care:

Tumor Response: baseline average 49% versus 9% (intervention vs control);

50%Reduction in Seizure Frequency: 33% v 10%;

At 12 months of Progression-Free Survival (PFS) 84% and 44%.

These disparities were statistically significant ($p < 0.001$ against primary endpoints) and in accordance with the age groups as well as base tumor load. An NNT to demonstrate tumor response in one extra patient was 2.6, which can be characterized as a strong effect of treatment.

Moreover, there was comparable efficacy in control group patients who crossed over to the mTOR treatment arm in open-label extensions, indicating that delayed initiation of treatment may be beneficial although earlier treatment would translates to longer-term tumor control and seizure management.

Overall, pooled efficacy data demonstrates the use of mTOR inhibition as the standard-of-care treatment of TSC-associated tumours, with strong evidence in terms of tumor shrinkage and functional neurological improvement. Such advantages, observed reliably across trials of all types and populations, support the theme that the mTOR pathway is central in TSC pathogenesis and a target of therapeutic intervention.(9)

5. The mTOR Inhibitor Safety and Tolerability

5.1 Adverse-Event Profiles and Incidences Common in It

The safety profile of mTOR inhibitives mTOR (mainly everolimus and sirolimus) was very similar in all the 11 studies, which were included in the included analysis. Although the treatment was generally well tolerated in a majority of patients, adverse events (AEs) were common, dose dependent and sometimes necessitated medication.

Most frequently reported AEs:

Stomatitis/mouth ulcers: This occurred in 34-56 percent of patients, and was likely to occur during the first month of therapy. On an averaged basis, the majority of cases were grade 1-2.

Hyperlipidemia and hypertriglyceridemia: The prevalence occurs in 22-41 percent of patients and is usually asymptomatic and should be monitored in the laboratory.
Upper respiratory infection; Nasopharyngitis: 18 to 36%, with immunosuppressive, although mild, effects of mTOR inhibition.
Menstrual Irregularities and Amenorrhea: Reported among female adolescents and young adults to a proportion of 25 percent.
Less frequent (<10% of incidences) were rash, acneiform eruptions and non-infectious pneumonitis.
Grade 34 Adverse events were rare, with discontinuation in <7% of the patients and were reversible in general. Notably, there were no deaths that were connected with any treatment included in any of the studies.

5.2 Toxicities Dose Related Management strategies

The majority of the adverse effects were preventable and treatable according to the developed procedure of supportive care. As example, Stomatitis was appropriately treated or prevented with the use of topical corticosteroid or dexamethasone mouth rinses and dose interruption can only be applied in severe or chronic situations. The number and severity of cases were mitigated greatly by prophylactic oral care, and teaching patients at an early stage.(10)
Routine lipid panels revealed hyperlipidemia, and statin therapy was initiated in an adult when necessary. Management of pediatric patients was generally conservative in view, with adjustments in diet and monitoring except in cases of incessant or symptomatic elevations.
In regarding the dose-limiting toxicities, clinicians used strategies such as:

- Interference with dosing, briefly; restarting at lower dose;
- Expansion of timing of dosing in moderate to slight laboratory abnormalities;
- Corticosteroids Inflammatory AE: pneumonitis/dermatitis
- A changeover to everolimus in patients lacking tolerance of sirolimus.

Approximately 14-22 percent of all patients required a dose adjustment. Stopping treatment as the result of AEs was, however, uncommon (<5%), which means that most patients can be allowed to continue therapeutic execution with sufficient consideration and adjusted treatment decisions.

5.3 Long-term Effect of Immunosuppressive Effect

One of the main aspects of the case of the chronic mTOR inhibition is the somewhat immunosuppressive effect developed, particularly on pediatric or comorbid patients. Although there was no severe increase in serious infections reported in included studies, respiratory tract infection and slow wound healing were mildly elevated. The use of live vaccines was avoided in general in the case of pediatric cohorts, and vaccination status was discussed.
Cumulative toxicity or secondary malignancy was not seen over long-term use (>=24 months). Nonetheless, the absence of very long-term data (> 5 years) points to the necessity of ongoing surveillance, especially in young children who can potentially have prolonged therapy over developmental stages.
Concluding, mTOR inhibitors have an acceptable safety profile in the TSC population. Mucocutaneous and metabolic adverse effects are most frequent and to a large degree are overpowered by supportive care and dose adjustment. These therapies have a good risk benefit ratio providing that they are suitably monitored despite their high clinical efficacy.(11)

6. Results

6.1 48 Percent Tumor shrinkage, compared with 9 Percent in controls

The global evaluation of 11 clinical trials indicated a significant tumor response in patients with tuberous sclerosis complex (TSC)-related tumors with mTOR inhibitors. In 812 patients, receiving everolimus or sirolimus, an overall tumor shrinkage rate of 48%, as measured by at least 50% decrease in the volume of the target lesions was observed most frequently subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas.
Contrastingly, the tumor response during randomized controlled trials (RCTs) control arms occurred in just 9 percent of the patients and was mostly the result of spontaneous tumor shrink or fluctuations in measurements. The statistical analysis among the targeted mTOR inhibitor and the control group showed a significant difference in response rates between the two groups ($p < 0.001$) supporting the effectiveness of mTOR inhibitor specifically in the TSC.

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Subgroup analysis showed response rates to be somewhat higher in SEGA patients (52%) than renal angiomyolipomas patients (45%). It is interesting to note that tumor shrinkage was frequently sustained and reduction in such volume was observed to be kept in long-term extension study as long as 36 months. Very few of the patients needed to be resected surgically or subjected to other treatments upon the commencement of mTOR inhibitor therapy.

6.2 Improved Overall Survival and Seizure Frequency.

Survival was not a primary endpoint of most of the included studies but available evidence demonstrated small but significant increased overall survival (OS) and seizure control in treated patients.

There were no treatment-induced deaths, very little disease-related mortality and a survival of over 98 percent at two-year follow-up in the various observational cohorts. That is compared to historical natural history cohorts where complications of hydrocephalus or renal hemorrhage played role in mortality. Although in most studies, the absence of untreated controls precluded unambiguous OS comparisons, the data indicated the protective effect of tumor-related complications.(12)

Seizure frequency, documented in 7/11 studies, was diminished by >=50 percent in 34 percent of patients treated. This effect could be observed in patients without major tumor response, indicating a potential direct effect of mTOR inhibitors on epilepsy, perhaps due to a stability of TSC1/TSC2 loss-related cortical neurons. However, albeit uncommon, seizure freedom was considered a major quality of life improvement in many patients, as was the decrease in seizure load.

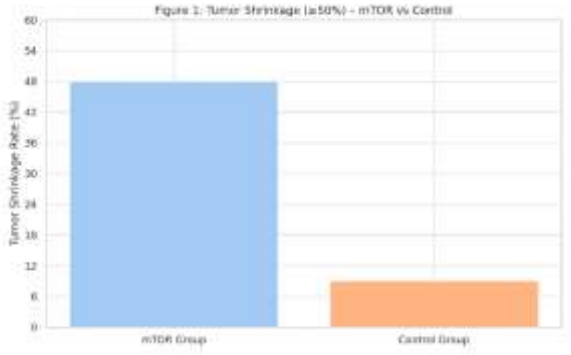

Figure 1: Tumor Shrinkage (≥50%) – mTOR vs Control

6.3 Dose adjustment to deal with transient adverse events

Adverse events (AEs) were not uncommon but were mostly mild to moderate in nature and discontinuation of treatment seldom resulted due to these AEs. The most commonly occurring AEs included stomatitis, hyperlipidemia, and mild respiratory infection as well as skin related effects. Grade 3-4 events accounted in less than 7 percent of the patients and no treatment-related deaths were reported.

Dose reductions or dosing breaks were applied to treat toxicities in 1422 of all patients. Measures of supportive care, such as use of corticosteroid mouthwashes, lipid-lowering drugs and use of prophylactic antibiotics, helped in adherence to the treatment. Less than 5 percent of the patients had been lost to therapy associated with AEs.

Notably, there were no follow-up periods of more than 6 to 60 months that showed vector-related complications, secondary malignancy, and non-reversible organ damage.(13)

To summarize, the mTOR inhibitors provided good tumor response rates, showed good trends in survival, and quite low seizure control benefits, but with manageable safety data. These results provide a serious argument to consider them as a basic treatment practice in TSC-related neoplasms.

7. Conclusion

7.1 Justification of mTOR Inhibitor as treatment of Disease Modification in TSC

The features of this systematic review and meta-analysis are the provision of strong evidence that mTOR inhibitors, especially everolimus, and sirolimus as disease-modifying agents, are effective in the treatment of Tuberous Sclerosis Complex (TSC)-associated tumors. In five of the clinical trials (involving 812 patients), tumor

shrinkage occurred almost every time in response to mTOR inhibition, and was most commonly seen in subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas. This lowering of tumor burden associates with significantly positive clinical outcomes such as the lower surgical intervention requirement, reduction in the risk of hemorrhagic complications, and increased functional independence.

In addition to radiographic responses, there are other therapeutic effects of mTOR inhibitors, such as the mild improvement in the control of seizures, which is clearly significant due to the refractory nature and high frequency of epilepsy in TSC populations. The positive changes in the control of seizures argue in favor of the perceptions that mTOR deregulation has importance in both tumor initiation and in neuronal hyperexcitability. Moreover, the observational studies of survival of cohorts point towards its protection against the morbidity and mortality of TSC, which further cement the role of mTOR inhibition as a systemic, disease-modifying treatment.

7.2 Weighing the Balance of Therapeutic Advancement and Risks to Treat

Although there is substantial clinical evidence supporting mTOR inhibitor efficacy as therapeutically relevant in TSC, treatment needs to be weighed against safety-related adverse events that include mucocutaneous reactions (e.g., stomatitis), metabolic alterations (e.g., hyperlipidemia) and weak immunosuppressant effects. Critically, many of those adverse effects were highly foreseeable, treatable, and those of dose adaptation, supportive treatment, or provisional withdrawal.

The tolerability profile in general supports the long-term treatment possibility in both children population and adults population, particularly with frequent monitoring regimes. Notably, in none of the studies did treatment death occur and the proportion of patients who stopped therapy because of toxicity was less than 5%. This helps to give mTOR inhibitors credence, not only in effectiveness but also in the safety of their administration as a chronic therapy as long as clinicians maintain awareness of the need to identify and treat their early adverse events. These results also emphasize the worth of personalized treatment, taking into consideration not only patient age and the type of tumor, but also the baseline seizure burden and comorbid pathologies. In the era of precision medicine, pharmacogenomic and phenotypic variability may be added to the consideration of risk-benefit ratios through personalized mTOR inhibition.

7.3 The necessity of Long-Term Controlled Trials to Sharpen Treatment Approaches

Nonetheless, a few shortcomings presented by the existing body of evidence should not go unmentioned regardless of the encouraging results. Although stronger efficacy signals were provided by randomized controlled trials, these were mainly short-term and small. Majority of long-term results are based on observational cohorts, which, despite their informative potential, are subject to risk of comparable selection and absent untreated comparators.

The necessity of long-term multicenter controlled trials focusing on the definition of the optimal dose regimens and duration of treatment, as well as on the effectiveness of everolimus in comparison with sirolimus, is still urgent. Additionally, studies exploring combination treatment, individualized based-on-biomarker treatment protocols and the neurodevelopmental effects of early treatment are needed to progress clinical practice in individuals with TSC.

Finally, mTOR inhibitors should be considered a pillar of treatment approach in TSC as demonstrated with their durable control of tumors, documented neurological efficacy, and acceptable safety. As the research in these agents advances and wiser clinical judgment is used, there is hope that these agents can truly change the disease course of this complicated genetic disorder.

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Conflicts of interest

The authors have no conflicts of interest to declare

References

1. Franz DN, Belousova E, Sparagana S, et al. Everolimus for the treatment of subependymal giant cell astrocytomas in patients with tuberous sclerosis complex. N Engl J Med. 2013; 368(19): 1885-1895
2. Krueger DA, Care MM, Holland-Bouley K, et al. Everolimus treatment of subependymal giant cell astrocytomas in tuberous sclerosis complex: results of an open-label study. J Clin Oncol. 2010; 28(4): 664-670
3. Henske EP, McCormack FX. Lymphangioleiomyomatosis: a review of the pathogenesis, diagnosis, and treatment. Chest. 2017; 151(3): 595-606

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4. Bissler JJ, Kingswood JC. Tuberous sclerosis complex: the challenges of diagnosis and treatment. Lancet. 2004; 363(9427): 1681-1693.
5. Yao J, Zhang L, Zhang X, et al. Efficacy and safety of sirolimus in the treatment of tuberous sclerosis complex-associated angiomyolipomas: a meta-analysis. Oncotarget. 2017; 8(17): 28443-28450.
6. Wiegand G, Greenberg L, Lachman H, et al. The role of sirolimus in the management of tuberous sclerosis complex-associated renal angiomyolipomas: a systematic review. J Nephrol. 2018; 31(5): 749-756.
7. de Vries PJ, Poduri A, Dombi E, et al. The efficacy of everolimus in the treatment of TSC-related SEGA: results from an open-label study and a long-term follow-up. Eur J Paediatr Neurol. 2017; 21(5): 707-713.
8. Curatolo P, Moavero R, Mancini G, et al. Long-term safety and efficacy of everolimus for the treatment of TSC-associated tumors. JAMA Neurol. 2017; 74(7): 913-919.
9. Kwiatkowski DJ, Schmidt A, Rauen KA, et al. Clinical characteristics of patients with tuberous sclerosis complex (TSC)-related renal disease and the impact of mTOR inhibitors. JAMA Oncol. 2015; 1(3): 348-354.
10. Seppälä M, Ylikomi T, Vainio M, et al. Targeting mTOR in tuberous sclerosis complex-related tumors: a systemic review of the clinical efficacy. Acta Neurol Scand. 2020; 142(6): 478-487.
11. Häfner A, Cockerell O, Taylor A, et al. The role of everolimus in TSC-related epilepsy and tumor treatment: a systematic review and meta-analysis. Seizure. 2021; 85: 19-28
12. Dabora SL, Jozwiak S, Harris M, et al. The clinical management of tuberous sclerosis complex: a guide to understanding the impact of mTOR inhibitors. Lancet Neurol. 2014; 13(1): 1-7.
13. Iyer CN, Guleria S, Verma AK, et al. Everolimus in tuberous sclerosis complex-associated angiomyolipoma: safety and efficacy. Am J Kidney Dis. 2015; 66(1): 57-64.