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Review article

Management of side effects of mTOR inhibitors in tuberous sclerosis patients

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ABSTRACT

mTOR inhibitors represent a relatively new therapeutic option in the management of patients affected by tuberous sclerosis complex (TSC). Randomized clinical trials support the use of everolimus in the treatment of subependymal giant cell astrocytomas (SEGA) and renal angiomyolipomas (AML) related to TSC. Accumulating data suggest also systemic disease-modifying potential of mTOR inhibitors.

Given that increasing number of patients with TSC receive mTOR inhibitors, the issue of adverse events associated with this therapy becomes practically important. In the present study we provide the overview of clinical manifestations and therapeutic options for the most common adverse events related to mTOR inhibitors in TSC patients.

Contents

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Introduction

The mammalian target of rapamycin (mTOR) is a protein kinase playing a key role in signaling pathway involved in numerous cellular processes including cell proliferation, survival, growth, metabolism, and plasticity [1] Dysregulation of mTOR pathway is emerging as a common theme in diverse human diseases, including tuberous sclerosis complex (TSC) [2].

TSC is a genetically determined disease characterized by the growth of benign tumors in various organs and systems [3]. In the course of TSC the brain, kidneys, liver, heart, retina of the eye, lungs, and skin may be affected.

Since the identification of *TSC1* gene locus coding for hamartin on chromosome 9q34 [4] in 1987 and the locus of *TSC2* gene coding tuberin on chromosome 16p13 [5] few years later, a substantial progress in understanding of molecular mechanisms underlying TSC has been made. Finding that tuberin plays an important role in mTOR signaling pathway [6] and further identification of tuberin-hamartin complex [7] as a main inhibitor of this pathway opened up new possibilities in disease-modifying therapy for TSC patients. mTOR overactivation has been confirmed in experimental models of TSC and rapamycin, an mTOR pathway inhibitor has been shown to reduce tumors in TSC rat model [8]. The positive effect of mTOR inhibitors has been also demonstrated in individuals with TSC. Rapamycin proved to be effective in the treatment of renal angiomyolipomas (AMLs) and subependymal giant cell astrocytomas (SEGAs) in small studies [9,10]. Phase III clinical trials EXIST-1 and EXIST-2 confirmed the efficacy of everolimus, another mTOR inhibitor, in the treatment of these tumors [11,12]. Growing evidence suggests that early mTOR inhibitor introduction might substantially modify TSC course in affected individuals [13]. The ongoing studies are designed to establish whether everolimus and rapamycin improve also epilepsy control and cognitive deficits in TSC patients.

Together with the increasing indications for mTOR inhibitors use in clinical practice the problem of adverse events related to this therapy has become practically important. Tumors associated with TSC regrow after mTOR inhibitors discontinuation, thus the patients might demand lifelong therapy to maintain the disease remission with adequately higher exposure to adverse events.

There is a substantial number of data on safety of mTOR inhibitors in cancer patients and transplant recipients, especially adults, however, considering the fact that constitutive overexpression of mTOR is a hallmark of TSC, the safety profile of rapamycin analogs (rapalogs) in TSC patients might be different. Moreover, in the present review we provide the concise description of mTOR inhibitors safety profile and their most common side effects in TSC patients according to epidemiological data from large clinical trials and own experience coming from pediatric population. We are also giving some practical management tips.

Characteristics of mTOR inhibitors

Rapamycin (sirolimus) is a prototype drug for all mTOR inhibitors [14]. Limitations in pharmacokinetic properties of rapamycin resulted in the search and identification of rapalogs. Everolimus (RAD-001), is the 40-*O*-(2-hydroxyethyl) derivative of rapamycin that has been developed for oral administration. Rapamycin contains no functional groups that ionize in the pH range 1–10 and therefore is substantially insoluble in water [15]. It has poor oral absorption and distributes widely in tissues, displaying not only a wide inter- and intrapatient variability in drug clearance, but also suboptimal correlations between whole blood concentrations and drug dose or patient characteristics [16]. Rapamycin is also characterized by the long half-life elimination of 60 h, in comparison to 30 h for everolimus. Oral everolimus is absorbed rapidly, and reaches peak concentration after 1.3–1.8 h [17]. Other rapalogs include temsirolimus and deforolimus and haven't been studied in TSC patients.

Regardless of the differences described above all rapalogs share the same mechanism of action. Rapamycin and rapalogs are small-molecule kinase inhibitors. The mode of action of this group of agents is to bind FKBP12. The rapamycin-FKBP12 complex inhibits the mTOR pathway by directly binding to mTORC1.

Safety profile of mTOR inhibitors

According to data provided by the European Medicines Agency [18] and FDA, everolimus (available for TSC patients as Votubia®, or Afinitor®, respectively) has two registered indications in TSC. Everolimus is indicated for the treatment of adult patients with renal AMLs associated with TSC who are at risk of complications (based on factors such as tumor size, presence of aneurysm, presence of multiple or bilateral tumors) but who do not require immediate surgery. Everolimus is also indicated for the treatment of patients, regardless of age, with SEGAs that require therapeutic intervention but are not amenable to surgery [19]. The drug is considered to be relatively safe. The most common side effects with everolimus (seen in more than 1 in 10 patients) are acne, stomatitis, upper respiratory tract infections, nasopharyngitis, sinusitis, pneumonia, increased blood level of cholesterol, irregular menstruation and amenorrhoea. The safety and efficacy of everolimus in children aged 0–18 years with renal AML associated with TSC in the absence of SEGA have not been established. Overall, there is a limited data on safety profile of everolimus in infants with TSC who require treatment for SEGA or cardiac rhabdomyoma [20–22]. The adverse events of mTOR inhibitors reported in TSC children and adults are similar in most of these studies [20–22]. There are no data on deleterious effect of mTOR inhibitors on physical development of children with TSC [22].

In the EXIST-1 study for SEGAs [11] everolimus proved to be a safe drug with limited number of side effects. Most adverse events were grade 1 or 2 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (AEs) [23]. The most common events were mouth ulceration, stomatitis, convulsion, and pyrexia. These disturbances were also most frequent among grade 3 adverse events. Grade 4 events were rare. Infections, mostly of the upper respiratory tract, were reported by 56 (72%) patients in the everolimus group and 26 (67%) in the placebo group. Apart from one (1%) case of grade 1 herpes zoster in the everolimus group, no opportunistic infections were reported; one (1%) infection (gastroenteritis in the everolimus group) was classified as grade 4. One (1%) patient in the everolimus group after 197 days of treatment had grade 2 interstitial pneumonitis that resolved fully 8 weeks after reduction of dose by one dose level. Thirty-eight (49%) patients in the everolimus group and four (10%) in the placebo group had adverse events requiring dose reduction or temporary interruption of treatment. The most common were stomatitis (observed in 13 [17%] patients in everolimus group *vs.* one [3%] patient in placebo group), mouth ulceration (six [8%] *vs.* 0), pyrexia (five [6%] *vs.* one [3%]), and pneumonia (four [5%] *vs.* 0). No adverse events led to discontinuation from the study, and none of the patients died during the study. In girls aged 13 years or older, three of eight in the everolimus group (aged 17 years, 19 years, and 19 years) and none of the five in the placebo group had secondary amenorrhea lasting from 8 weeks to 14 months. Two cases resolved without intervention, and one resolved after progesterone.

In a recent 5-year analysis of everolimus treatment in TSC patients with SEGAs this therapeutic approach continues to demonstrate a sustained effect on SEGA tumor reduction over ≥5 years of treatment [24]. Most commonly reported AEs were