Everolimus

Everolimus (INN) (/ˌɛvəˈroʊsləməs/) (earlier code name **RAD001**) is the 40-*O*-(2-hydroxyethyl) derivative of sirolimus and works similarly to sirolimus as an inhibitor of mammalian target of rapamycin (mTOR).

It is currently used as an immunosuppressant to prevent rejection of organ transplants and treatment of renal cell cancer and other tumours. Much research has also been conducted on everolimus and other mTOR inhibitors as targeted therapy for use in a number of cancers.

It is marketed by Novartis under the tradenames **Zortress** (USA) and **Certican** (Europe and other countries) in transplantation medicine, and as **Afinitor** (general tumours) and **Votubia** (tumours as a result of TSC) in oncology. Everolimus is also available from Biocon, with the brand name *Evertor, from Natco Pharma, with the brand name Temonat, from Ranbaxy Laboratories, with the brand name of Imozide, from Emcure Pharmaceuticals, with the brand name of Temcure, among over 20 different brands*.

1 Approvals and indications

Everolimus is approved for various conditions:

- Advanced kidney cancer (US FDA approved in March 2009)[2]
- Prevention of organ rejection after renal transplant(US FDA April 2010)[3]
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in patients who are not suitable for surgical intervention (US FDA October 2010)[4]
- Progressive or metastatic pancreatic neuroendocrine tumors not surgically removable (May 2011)[5]
- Breast cancer in post-menopausal women with advanced hormone-receptor positive, HER2-negative type cancer, in conjunction with exemestane (US FDA July 2012)[6]
- Prevention of organ rejection after liver transplant(Feb 2013)
- Progressive, well-differentiated non-functional, neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease (US FDA February 2016).[7]

2 UK National Health Service

NHS England has been criticised for delays in deciding on a policy for the prescription of Everolimus in the treatment of Tuberous Sclerosis. 20 doctors addressed a letter to the board in support of the charity Tuberous Scelerosis Association saying " around 32 patients with critical need, whose doctors believe everolimus treatment is their best or only option, have no hope of access to funding. Most have been waiting many months. Approximately half of these patients are at imminent risk of a catastrophic event (renal bleed or kidney failure) with a high risk of preventable death."[8] In May 2015 it was reported that Luke Henry and Stephanie Rudwick, the parents of a child suffering from Tuberous Sclerosis were trying to sell their home in Brighton to raise £30,000 to pay for treatment for their daughter Bethany who has tumours on her brain, kidneys and liver and suffers from up to 50 epileptic fits a day.[9]

3 Clinical trials

As of October 2010, Phase III trials are under way in gastric cancer, hepatocellular carcinoma and lymphoma.[10] The use of everolimus in refractory chronic graft-versus-host disease has been reported in 2012.[11]

Interim phase III trial results in 2011 showed that adding Afinitor (everolimus) to exemestane therapy against advanced breast cancer can significantly improve progression-free survival compared with exemestane therapy alone.[12]

Furthermore, there is a study that shows that there is a different sensitivity to everolimus between patients depending on their genome.[13] Through a Phase II clinical trial done in patients that presented advanced metastasic bladder carcinoma (NCT00805129) [14] they found just one person that positively responded to everolimus treatment for 26 months. Thus, they decided to sequence the genome of this patient and to compare it to different reference genomes and to other patients' genomes. This way, they discovered that mutations in TSC1 lead to an increase in recurrence and to an increase in the response time to everolimus. Thus, it has been determined that everolimus is more efficient in those patients that present somatic mutations in TSC1.

4 Mechanism

In a similar fashion to other mTOR inhibitors its effect is solely on the mTORC1 protein complex and not on the mTORC2 complex. This can lead to a hyper-activation of the kinase AKT via inhibition on the mTORC1 negative feedback loop while not inhibiting the mTORC2 positive feedback to AKT. This AKT elevation can lead to longer survival in some cell types. Hence, everolimus has an important effect on cell growth, cell proliferation and cell survival. mTORC1 action is modulated by several mitogens, growth factors and nutrients.

TSC1 and TSC2 (which are the genes involved in tuberous sclerosis disease) act as tumor suppressor genes by regulating mTORC1 activity. Thus, either the loss or inactivation of one of these genes lead to the activation of mTORC1.[15]

Everolimus binds to its protein receptor FKBP12, which directly interacts with mTORC1 inhibiting its downstream signaling. As a consequence, mRNAs that codify proteins implicated in the cell cycle and in the glycolysis process are impaired or altered, so tumor growth is inhibited. Hence, everolimus inhibits tumor cells' growth and proliferation.[15]

5 Adverse reactions

A trial using 10 mg/day in patients with NETs of GI or lung origin reported "Everolimus was discontinued for adverse reactions in 29% of patients and dose reduction or delay was required in 70% of everolimus-treated patients. Serious adverse reactions occurred in 42% of everolimus-treated patients and included 3 fatal events (cardiac failure, respiratory failure, and septic shock). The most common adverse reactions (incidence greater than or equal to 30%) were stomatitis, infections, diarrhea, peripheral edema, fatigue and rash. The most common laboratory abnormalities (incidence greater than or equal to 50%) were anemia, hypercholesterolemia, lymphopenia, elevated aspartate transaminase (AST) and fasting hyperglycemia.".[7]

6 Role in heart transplantation

Everolimus may have a role in heart transplantation as it has been shown to reduce chronic allograft vasculopathy in such transplants. It also may have a similar role to sirolimus in kidney and other transplants.[16]

7 Role in Liver Transplantation

Although, sirolimus, an m-TOR inhibior had generated worries initially while using m-TORs in liver transplantation recipients due to possible early hepatic artery thrombosis and graft loss, use of Everolimus in the setting of liver transplantation is promising. Recent studies have proven the safety of the everolimus when used in early phase after liver transplantation. Jeng et al.[17] in their study of 43 patients concluded the safety of use of everolimus in early phase after living donor liver transplantation. In their study no hepatic artery thrombosis or wound infection was noted. Also, a possible role of everolimus in reducing the recurrence of hepatocellular carcinoma after liver transplantation was correlated. At a target trough level of 3 ng/mL at 3 months was proved to be beneficial in recipients with pre-transplant renal dysfucntion. In their study, 6 of 9 renal failure patients showed significant recovery of renal function, whereas 3 of them showed further deterioration and 1 required hemodialysis. The same study group claims decreased recurrence of hepatocelullar carcinoma recurrence if everolimus was used in early phase after transplantation.[18]

8 Use in vascular stents

Everolimus is used in drug-eluting coronary stents as an immunosuppressant to prevent restenosis. Abbott Vascular produces an everolimus-eluting stent (EES) called Xience Alpine. It utilizes the Multi-Link Vision cobalt chromium stent platform and Novartis' everolimus. The product is widely available gobally including USA, Europe, and APAC countries. Boston Scientific also market EES' of which they currently have Promus Premiere and Synergy versions.

9 Use in aging

Inhibition of mTOR, the molecular target of Everolimus, extends the lifespan of model organisms including mice,[19] and mTOR inhibition has been suggested as an anti-aging therapy. Everolimus was used in a recent clinical trial by Novartis, and short-term treatment was shown to enhance the response to the influenza vaccine in the elderly, possible by reversing immunosenescence.[20] Everolimus treatment of mice results in reduced metabolic side effects compared to sirolimus.[21]

10 See also

- Discovery and development of mTOR inhibitors

11 References

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12 External links

- Sedrani R, Cottens S, Kallen J, Schuler W (August 1998). "Chemical modification of rapamycin: the discovery of SDZ RAD". *Transplant. Proc.* **30** (5): 2192–4. doi:10.1016/S0041-1345(98)00587-9. PMID 9723437.

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