Preclinical evidences suggest new treatment options for endocrine disorders: Pasireotide (SOM230) and Everolimus (RAD001)

Données précliniques suggérant de nouvelles options thérapeutiques des désordres endocriniens : l’exemple du Pasiréotide (SOM230) et l’Éverolimus (RAD001)

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Pasireotide (SOM230) is a new somatostatin (sst) analog which binds with nanomolar affinity to sst1, 2, 3 and 5 receptors, in contrast to the clinically available compounds octreotide and lanreotide, which bind preferably to sst2 [1,6]. Pasireotide potently suppresses GH, IGF-1 and ACTH secretion, indicating potential efficacy in acromegaly and Cushing’s disease [7,9,12]. In studies directly comparing the inhibitory effects of pasireotide and octreotide on GH and IGF-1 secretion, the long term application of pasireotide resulted in a more potent and longer lasting inhibitory effect than octreotide [1,7,8]. The expression of sst5 receptors seems to be crucial for the inhibitory effect of pasireotide on GH secretion in those acromegalic patients in which octreotide was not or only partially effective [11]. The prime importance of the sst5 receptor subtype in ACTH secreting pituitary tumors has recently been described by Hofland et al. [3]. They showed that in the majority of corticotroph adenomas from Cushing’s patients the sst5 expression is high, whereas the sst2 expression is low. One reason for the selective sst5 expression in Cushing’s patients might be that the expression of sst2 is downregulated by long-term cortisol, whereas the expression of sst5 is resistant to long-term cortisol [12]. In rats, s.c. application of pasireotide resulted in a stronger inhibition of ACTH and corticosterone than octreotide [9]. The expression of multiple sst receptors in carcinoid tumors suggests that pasireotide may have clinical advantages over octreotide also in patients with carcinoid tumors. Typically, patients with gastroenteropancreatic neuroendocrine tumors (GEP/NET) who’s symptoms are initially well-controlled by octreotide develop tachyphylaxis during prolonged treatment. Rats, in contrast to humans, develop tachyphylaxis to the inhibitory effect of octreotide on GH and IGF-1 secretion after three to five days of treatment. Under these conditions, the infusion of pasireotide resulted in a strong and non desensitizing inhibition of secretion [1,8]. Direct and indirect antitumor activity has been observed in vivo and in vitro with pasireotide, suggesting a possible role for pasireotide in antineoplastic therapy. However, effects seen in several animal modes seem to be small compared to the pronounced antiproliferative effect observed with octreotide and pasireotide in recent clinical studies in acromegaly and Cushing’s patients [2,8].

Everolimus (RAD001) is an orally active inhibitor of the mammalian target of rapamycin (mTOR), which is an intracellular kinase that acts as a central regulator of multiple signaling pathways (IGF, EGF, PDGF, VEGF, amino acids) that mediate abnormal growth, proliferation, survival and angiogenesis in cancer. mTOR is a critical component of the PI3K/AKT pathway, a key signaling pathway that is frequently dysregulated in many cancers. In fact, overexpression and activation of Akt has been observed in human pituitary adenomas [4] and IGF-1 was found to be an endocrine and autocrine activator of the PI3K/AKT/mTOR pathway in GEP/NET tumors [5,13]. Interestingly, inhibition of mTOR stimulates a negative feed back-loop resulting in activation of Akt [5]. Inhibition of IGF-1 receptor or PI3 kinase prevents the Rapamycin induced Akt activation and may thus sensitize tumor cells to the antiproliferative effect of RAD001 [4,5,10]. In BON-1 neuroendocrine tumor cells RAD001 inhibited proliferation which was dependent on the serum concentration in the medium [15], supporting the view that stimulating the growth factor receptor pathway reduces the efficacy of RAD001. In summary, these data suggest that RAD001 might be a useful compound for the treatment of neuroendocrine as well as pituitary tumors. The combination

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of RAD001 and somatostatin analogues in the treatment of GEP/NET and pituitary tumors offers promising treatment options, by simultaneously controlling the hypersecretion of hormones as well as tumor growth. In addition, SOM230 has the potential to increase the antiproliferative potency of RAD001 due to its strong and long lasting inhibitory effect on GH, IGF-1 and other growth factors, which stimulate the growth factor/PI3/AKT pathway. Preliminary clinical studies investigating the combined effect of octreotide and RAD001 in GEP/NET show tumor reduction and PFS in the majority of patients [14].

References