REVIEW

Pasireotide in the treatment of neuroendocrine tumors: a review of the literature

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Abstract

Somatostatin analogs have an important role in the medical therapy of neuroendocrine tumors (NETs). Octreotide and lanreotide, both somatostatin analogs binding with high affinity for the somatostatin receptor (SSTR)2, can control symptoms in functional NETs. In addition, these compounds, because of their antiproliferative effects, can stabilize growth of well-differentiated NETs. Pasireotide is a novel multireceptor-targeted somatostatin analog with high affinity for SSTR1, 2, 3, and 5. This review provides an overview of the state of the art of pasireotide in the treatment of NETs, with the aim of addressing clinical relevance and future perspectives for this molecule in the management of NETs.

Introduction

Neuroendocrine tumors (NETs) comprise a heterogeneous group of neoplasms in most cases with a low rate of growth and sometimes able to produce and secrete several hormones that drive forward specific clinical syndromes, leading to significant disability and a negative impact on quality of life. Several therapeutic options for NETs are available and a multidisciplinary approach is needed for a proper management of this disease. The current first-line therapy of these neoplasms is represented by surgery followed by medical management, such as somatostatin analogs (SSAs), mTOR inhibitors, tyrosine kinase inhibitors, chemotherapy and peptide receptor radionuclide therapy. However, new treatment options to further improve survival outcomes are needed (Walenkamp et al. 2014). Somatostatin receptors (SSTRs) are expressed in NETs and SSAs are widely used as medical therapy both in functioning and non-functioning well-differentiated NETs. Octreotide long-acting release and lanreotide autogel are the two first-generation long-acting SSAs currently approved for the treatment of well-differentiated NETs. These SSAs, characterized by a restricted affinity profile for SSTR2 and at lesser extent SSTR5, inhibit hormonal secretion and provide an effective control of hypersecretion symptoms in about 40–60% of patients with functioning NETs (Pavel et al. 2017, Mazziotti et al. 2017). In addition, two prospective multicenter randomized clinical trials (PROMID and CLARINET) demonstrated that both SSAs have antiproliferative activity in the management of advanced NETs. Indeed, although SSAs have limited activity in terms of tumor shrinkage, they are able to stabilize tumor proliferation, leading to a significant

Pasireotide is a second-generation multireceptor-targeted SSA with a broader spectrum of affinity with respect to octreotide and lanreotide for different receptor subtypes (SSTR1, 2, 3, 5). Pasireotide is currently approved for the treatment of acromegaly and Cushing’s disease. This paper provides a state-of-the-art overview of pasireotide in the treatment of NETs, with the aim of addressing clinical relevance and future perspectives for this molecule in the management of NETs.

Expression of SSTR subtypes in NETs

Several studies have identified the expression of SSTRs in NET cell lines, primary NETs cell cultures and tissues through a variety of techniques including reverse transcriptase polymerase chain reaction (RT-PCR), in situ hybridization (ISH), immunohistochemistry (IHC) and autoradiography (Table 1).

In most of these studies, SSTR mRNA expression was evaluated by RT-PCR. The characterization of pancreatic NET primary cultures from 15 patients showed expression of SSTR1 and SSTR2 mRNAs in all cases, with a higher SSTR2 expression level compared to SSTR1 in 80% of cases. SSTR3 and SSTR5 mRNAs were expressed in 73 and 67% of cases, respectively. A different expression of SSTR5 was observed in relation to the WHO histological grade of the tumor (100% in grade 1, only 37% in grade 2 tumors) (Mohamed et al. 2014). Also, in another series of pancreatic and gastrointestinal NETs, SSTR1 and SSTR2 mRNA were the most commonly detected subtypes (over 80%), followed by SSTR3 and SSTR5. Poorly differentiated NETs showed a reduced SSTR expression (Papotti et al. 2002). In pancreatic NET cell lines (BON-1 and QGP-1), mRNA levels of SSTRs were expressed in the following order: SSTR5 > SSTR1 > SSTR2 > SSTR3, but in QGP-1 cells, the expression of SSTR3 was not detectable (van Adrichem et al. 2016). ISH confirmed the expression of SSTR1 and SSTR2 mRNA in about 50–70% of gastroenteropancreatic (GEP) NETs (Reubi et al. 1994, Janson et al. 1996).

IHC and autoradiography confirmed that SSTRs 1, 2 and 5 were the most frequent receptors in GEP NETs, whereas the expression of SSTR3 was quite variable (Kimura et al. 1999, Kulaksiz et al. 2002, Papotti et al. 2002, Bertherat et al. 2003, Reubi & Waser 2003, Yerci et al. 2015, Kasajima et al. 2017).

In lung NETs, SSTR1 and SSTR2 were the most expressed subtypes, followed by SSTR3. The expression of SSTR5 varied from 0 to 63% of tumors and SSTR4 resulted to be rarely expressed. SSTRs showed a decreased protein expression from well to poorly differentiated pulmonary neuroendocrine carcinomas (Reubi & Waser 2003, Righi et al. 2010, Tsuta et al. 2012, Kanakis et al. 2015).

In primary pheochromocytoma, cell cultures and tissues SSTRs were expressed at mRNA level with a prevalent expression of SSTR2 and SSTR5 (Pasquali et al. 2008). Also, in another paper, SSTR2 mRNA was the most frequently detected subtype in pheochromocytoma and paraganglioma tissues (SSTR2 > SSTR1 > SSTR3 and SSTR5) (Saveanu et al. 2011). Other studies found at IHC that SSTR3 was the predominant receptor subtype in both malignant and benign pheochromocytomas and SSTR2A was expressed in less than one-third of pheochromocytoma and preferentially in benign lesions (Mundschenk et al. 2003, Unger et al. 2008).

Although the highly variable expression of SSTR subtypes reported in these studies and depending on the methodology adopted, the majority of NETs expresses several SSTRs subtypes. This has paved the way to the development of new SSTR panligands, such as pasireotide, which display a broader receptor-binding profile compared with octreotide and lanreotide.

After activation, SSTRs modulate different intracellular effectors, mediating antisecretory and antiproliferative effects of SSAs in NETs (Fig. 1). In particular, antisecretory activity is exerted via decrease of cAMP levels and calcium channel activity. The activation of phosphotyrosine phosphatases, such as SRC homology phosphatase type 1 and type 2, density-enhanced protein-tyrosine phosphatase-1, and the modulation of mitogen-activated protein kinase (MAPK) activity are mainly involved in antiproliferative effects of SSTRs. Both adenylyl cyclase inhibition and phosphotyrosine phosphatases activation are induced by all SSTRs, while MAPK activity depends on SSTR subtype since it is increased by SSTR4, decreased by SSTR3 and 5 and modulated in both directions by SSTR1 and 2. Indeed, different conformations of the receptor–SSA complex are the reason of the selective activation of different pathways and of the modulation of receptor endocytosis (Barbieri et al. 2014).

Pasireotide as a single-agent treatment in NETs

Preclinical studies

In 2004, Schmid & Schoeffter showed that pasireotide inhibits forskolin-stimulated cAMP accumulation with similar efficacy of somatostatin (SRIF-14) in CCL39 cells
### Table 1  Expression of somatostatin receptor (SSTR) subtypes in neuroendocrine tumors (NETs), evaluated through different methods.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>SSTR1 (%)</th>
<th>SSTR2 (%)</th>
<th>SSTR3 (%)</th>
<th>SSTR4 (%)</th>
<th>SSTR5 (%)</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic NETs (n=15)</td>
<td>100</td>
<td>100</td>
<td>73</td>
<td>–</td>
<td>67</td>
<td>RT-PCR</td>
<td>Mohamed et al. (2014)</td>
</tr>
<tr>
<td>Pancreatic NETs (n=33)</td>
<td>90.1</td>
<td>84.8</td>
<td>78.8</td>
<td>24.2</td>
<td>42.4</td>
<td>RT-PCR</td>
<td>Papotti et al. (2002)</td>
</tr>
<tr>
<td>GI NETs (n=13)</td>
<td>92.3</td>
<td>100</td>
<td>53.8</td>
<td>15.4</td>
<td>76.9</td>
<td>RT-PCR</td>
<td>Papotti et al. (2002)</td>
</tr>
<tr>
<td>Pancreatic NETs (n=22)</td>
<td>–</td>
<td>68.2</td>
<td>36.4</td>
<td>–</td>
<td>63.6</td>
<td>Autoradiography</td>
<td>Papotti et al. (2002)</td>
</tr>
<tr>
<td>GI NETs (n=15)</td>
<td>–</td>
<td>80</td>
<td>60</td>
<td>–</td>
<td>80</td>
<td>IHC</td>
<td>Papotti et al. (2002)</td>
</tr>
<tr>
<td>GEP NETs (n=17)</td>
<td>47</td>
<td>65</td>
<td>35</td>
<td>–</td>
<td>–</td>
<td>ISH</td>
<td>Reubi et al. (1994)</td>
</tr>
<tr>
<td>GI NETs (n=25)</td>
<td>68</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ISH</td>
<td>Janson et al. (1996)</td>
</tr>
<tr>
<td>Pancreatic NETs (n=16)</td>
<td>–</td>
<td>94 (2A)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>IHC</td>
<td>Kimura et al. (1999)</td>
</tr>
<tr>
<td>Pancreatic NETs (n=21)</td>
<td>–</td>
<td>85.7</td>
<td>–</td>
<td>–</td>
<td>61.9</td>
<td>IHC</td>
<td>Yerci et al. (2015)</td>
</tr>
<tr>
<td>Stomach NETs (n=8)</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>37.5</td>
<td>IHC</td>
<td>Yerci et al. (2015)</td>
</tr>
<tr>
<td>Small bowel NETs (n=10)</td>
<td>–</td>
<td>70</td>
<td>–</td>
<td>–</td>
<td>70</td>
<td>IHC</td>
<td>Yerci et al. (2015)</td>
</tr>
<tr>
<td>Appendix NETs (n=7)</td>
<td>–</td>
<td>85.7</td>
<td>–</td>
<td>–</td>
<td>71.5</td>
<td>IHC</td>
<td>Yerci et al. (2015)</td>
</tr>
<tr>
<td>Rectum NETs (n=3)</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>66.6</td>
<td>IHC</td>
<td>Yerci et al. (2015)</td>
</tr>
<tr>
<td>Gastrinoma (n=33)</td>
<td>30</td>
<td>100 (2A)</td>
<td>79</td>
<td>–</td>
<td>76</td>
<td>IHC</td>
<td>Kulaksiz et al. (2002)</td>
</tr>
<tr>
<td>Insulinoma (n=36)</td>
<td>31</td>
<td>58 (2A)</td>
<td>78</td>
<td>–</td>
<td>78</td>
<td>IHC</td>
<td>Kulaksiz et al. (2002)</td>
</tr>
<tr>
<td>Carcinoid tumor (n=35)</td>
<td>37</td>
<td>86 (2A)</td>
<td>71</td>
<td>–</td>
<td>83</td>
<td>IHC</td>
<td>Kulaksiz et al. (2002)</td>
</tr>
<tr>
<td>NETs (n=52)</td>
<td>–</td>
<td>73 (2A)</td>
<td>–</td>
<td>–</td>
<td>25</td>
<td>IHC</td>
<td>Kasajima et al. (2017)</td>
</tr>
<tr>
<td>Insulinoma (n=20)</td>
<td>44</td>
<td>72</td>
<td>44</td>
<td>28</td>
<td>72</td>
<td>Autoradiography</td>
<td>Bertherat et al. (2003)</td>
</tr>
<tr>
<td>Insulinoma (n=18)</td>
<td>52</td>
<td>96</td>
<td>15</td>
<td>4</td>
<td>48</td>
<td>Autoradiography</td>
<td>Reubi &amp; Waser (2003)</td>
</tr>
<tr>
<td>Ileal NETs (n=27)</td>
<td>61</td>
<td>69</td>
<td>35</td>
<td>4</td>
<td>20</td>
<td>Autoradiography</td>
<td>Reubi &amp; Waser (2003)</td>
</tr>
<tr>
<td>Gastrinoma (n=10)</td>
<td>10</td>
<td>100</td>
<td>20</td>
<td>0</td>
<td>33</td>
<td>Autoradiography</td>
<td>Reubi &amp; Waser (2003)</td>
</tr>
<tr>
<td>Glucagonoma (n=4)</td>
<td>67</td>
<td>67</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>Autoradiography</td>
<td>Reubi &amp; Waser (2003)</td>
</tr>
<tr>
<td>VIPoma (n=4)</td>
<td>25</td>
<td>100</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>Autoradiography</td>
<td>Reubi &amp; Waser (2003)</td>
</tr>
<tr>
<td>Lung carcinoid (n=29)</td>
<td>71</td>
<td>68</td>
<td>3</td>
<td>0</td>
<td>23</td>
<td>Autoradiography</td>
<td>Reubi &amp; Waser (2003)</td>
</tr>
<tr>
<td>Typical carcinoid (n=57)</td>
<td>79</td>
<td>96 (2A)</td>
<td>49</td>
<td>5</td>
<td>0</td>
<td>IHC</td>
<td>Tsuta et al. (2012)</td>
</tr>
<tr>
<td>Atypical carcinoid (n=11)</td>
<td>77</td>
<td>77 (2A)</td>
<td>77 (2B)</td>
<td>33</td>
<td>0</td>
<td>IHC</td>
<td>Tsuta et al. (2012)</td>
</tr>
<tr>
<td>Large cell NEC (n=21)</td>
<td>60</td>
<td>60 (2A)</td>
<td>30 (2B)</td>
<td>40</td>
<td>0</td>
<td>15</td>
<td>IHC</td>
</tr>
<tr>
<td>Small-cell carcinoma (n=57)</td>
<td>27</td>
<td>69 (2A)</td>
<td>24 (2B)</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>IHC</td>
</tr>
<tr>
<td>Lung carcinoid (n=119)</td>
<td>63</td>
<td>72 (2A)</td>
<td>20</td>
<td>0</td>
<td>40</td>
<td>IHC</td>
<td>Kanakis et al. (2015)</td>
</tr>
<tr>
<td>Lung carcinoid (n=11)</td>
<td>88</td>
<td>88 (2A)</td>
<td>12.5</td>
<td>0</td>
<td>63</td>
<td>RT-PCR</td>
<td>Kanakis et al. (2015)</td>
</tr>
<tr>
<td>Typical carcinoid (n=41)</td>
<td>34</td>
<td>2A</td>
<td>66</td>
<td>–</td>
<td>–</td>
<td>IHC</td>
<td>Righi et al. (2010)</td>
</tr>
<tr>
<td>Typical carcinoid with metastases (n=24)</td>
<td>71</td>
<td>72 (2A)</td>
<td>58</td>
<td>–</td>
<td>–</td>
<td>IHC</td>
<td>Righi et al. (2010)</td>
</tr>
<tr>
<td>Atypical carcinoid (n=73)</td>
<td>–</td>
<td>51 (2A)</td>
<td>45</td>
<td>–</td>
<td>–</td>
<td>IHC</td>
<td>Righi et al. (2010)</td>
</tr>
<tr>
<td>Large cell NEC (n=60)</td>
<td>–</td>
<td>33 (2A)</td>
<td>33</td>
<td>–</td>
<td>–</td>
<td>IHC</td>
<td>Righi et al. (2010)</td>
</tr>
<tr>
<td>Small-cell carcinoma (n=61)</td>
<td>–</td>
<td>38 (2A)</td>
<td>29</td>
<td>–</td>
<td>–</td>
<td>IHC</td>
<td>Righi et al. (2010)</td>
</tr>
<tr>
<td>Pheochromocytoma (n=6)</td>
<td>83</td>
<td>100</td>
<td>82</td>
<td>83</td>
<td>100</td>
<td>RT-PCR</td>
<td>Pasquali et al. (2008)</td>
</tr>
<tr>
<td>Pheochromocytoma (n=39)</td>
<td>95</td>
<td>100</td>
<td>56</td>
<td>–</td>
<td>54</td>
<td>RT-PCR</td>
<td>Saveau et al. (2011)</td>
</tr>
<tr>
<td>Paraganglioma (n=13)</td>
<td>92</td>
<td>100</td>
<td>31</td>
<td>–</td>
<td>31</td>
<td>RT-PCR</td>
<td>Saveau et al. (2011)</td>
</tr>
<tr>
<td>GEP NETs (n=35)</td>
<td>100</td>
<td>100</td>
<td>63</td>
<td>–</td>
<td>89</td>
<td>RT-PCR</td>
<td>Mundschenk et al. (2003)</td>
</tr>
<tr>
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<td>8</td>
<td>25 (2A)</td>
<td>90</td>
<td>10</td>
<td>15</td>
<td>IHC</td>
<td>Unger et al. (2008)</td>
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<tr>
<td>Benign Pheochromocytoma (n=7)</td>
<td>29</td>
<td>29 (2A)</td>
<td>100</td>
<td>0</td>
<td>29</td>
<td>IHC</td>
<td>Unger et al. (2008)</td>
</tr>
<tr>
<td>Malignant Pheochromocytoma (n=8)</td>
<td>0</td>
<td>0 (2A)</td>
<td>75</td>
<td>13</td>
<td>38</td>
<td>IHC</td>
<td>Unger et al. (2008)</td>
</tr>
</tbody>
</table>

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(Chinese hamster lung fibroblasts), stably transfected with the human SSTR1 gene, and in CHOK1 cells (Chinese hamster ovary), stably transfected with the human SSTR2, SSTR3 and SSTR5 genes. This effect was more potent than that reported with octreotide (Schmid & Schoeffter 2004).

Several further studies described in vitro a significant antitumor activity of pasireotide in NET cells. Ono et al. reported a more potent antiproliferative effect and decrease in Ki-67 after incubation of NCI-H727 cells, a bronchial NET cell line, with pasireotide compared to the untreated control and the conventional octreotide...
(Ono et al. 2007). van Adrichem et al. showed that pasireotide statistically inhibited bioactivity of insulin receptor isoforms A (IRA) in BON-1 cells, evaluated by KIRA assay, while no effect was observed during incubation with octreotide (van Adrichem et al. 2016). In primary pheochromocytoma cell cultures, both octreotide and pasireotide induced a significant reduction in cell viability and catecholamine production and an increase in apoptotic cells. These effects were more potent with pasireotide than with octreotide (Pasquali et al. 2008).

In pancreatic NET primary cell cultures, octreotide and pasireotide similarly reduced cell proliferation through induction of apoptosis, decreased chromogranin A (CgA) secretion in a dose-dependent manner and reduced CAMP levels. Interestingly, a different SSTR2 trafficking was observed during incubation of NET cells with octreotide and pasireotide. After 5 min octreotide induced the SSTR2 internalization, maintained in the cytosol up to 30 min, this trafficking was associated with phosphorylation on Ser341/343 of SSTR2. Pasireotide induced a rapid and transient internalization of SSTR2. After 5 min of incubation with pasireotide, SSTR2 was internalized, but after 15 min, it was observed at the cell surface and no phosphorylation on Ser341/343 of SSTR2 was detected. The rapid recycling of the SSTR2 and the lack of Ser phosphorylation, crucial for the SSTR2 desensitization, underlined that the level of active receptors at the cell surface was greater with pasireotide than with octreotide. These data suggest a possible benefit in the long-term treatment with pasireotide (Mohamed et al. 2014).

In a mouse model of multiple endocrine neoplasia type 1 (Men1), where mice deleted for an allele of the Men1 gene (Men1+/−) develop pancreatic NETS (positive for insulin) and pituitary adenomas (predominantly prolactinomas but also somatotrophinomas and non-functioning adenomas), the antitumor activity of pasireotide has been evaluated. In these animals, pancreatic NETs expressed SSTR1, 2 and 5. Treatment of Men1+/− mice with pasireotide decreased proliferation in pancreatic and pituitary NETs through induction in apoptosis. Men1+/− mice treated with pasireotide showed an increased survival. In addition, pasireotide decreased development of pancreatic NETs and size of pituitary adenomas. These results suggest that pasireotide may have a chemopreventive role in the treatment of MEN1-associated NETs (Walls et al. 2016).

In another Men1 transgenic mouse model adopting pancreas-specific promoter (Pdx1) in combination with Cre-Lox system to knockout Men1 in pancreas of mice (Pdx1-Cre:Men1 floxed/floxed) and able to develop insulinoma, pasireotide decreased insulin levels and improved serum glucose levels compared to the untreated control group. In addition, pasireotide stimulated apoptosis and reduced the tumor size of insulinoma (Quinn et al. 2012).

Clinical studies

Octreotide and lanreotide inhibit the release of bioactive hormones and significantly improve diarrhea and flushing in most of patients with the carcinoid syndrome (Rusziewski et al. 2004, Modlin et al. 2010). However, long-term use of these agents is limited by tachyphylaxis, occurring in a considerable number of patients within 1 year after beginning of treatment (Hofland & Lamberts 2003). Pasireotide has been tested as a monotherapy for the management of diarrhea and flushing in patients with carcinoid syndrome resistant to first-generation SSAs at conventional doses. In a phase II, open-label, multicenter, prospective single-arm study (Kvols et al. 2012), 44 patients with advanced NETs of the gastrointestinal tract and poorly controlled carcinoid syndrome during therapy with octreotide LAR received s.c. pasireotide up to 1200 µg twice daily. Levels of tumor markers (urinary 5-hydroxyindole acetic acid and serum chromogranin A) rapidly decreased after pasireotide initiation and remained low. In 12 (27%) of these patients, pasireotide achieved at least partial control of symptoms when administered at doses of 600–900 mg twice daily for 15 consecutive days. A similar proportion of patients (20.9%) achieved symptom control after 6 months of pasireotide treatment in a phase III multicenter study (Wolin et al. 2015) randomizing patients with metastatic gastrointestinal NETs and inadequately controlled carcinoid symptoms under first-generation SSAs (octreotide LAR 30 mg/28 days, octreotide s.c. 600 µg/day, lanreotide autogel 120 mg/28 days or lanreotide SR 30 mg/14 days). Subjects were randomized to receive pasireotide LAR 60 mg or high-dose octreotide LAR (40 mg every 28 days). However, this study was halted before completion due to a low predictive probability of showing differences in symptom control between treatment arms (odds ratio (OR) 0.73; 95% confidence interval (CI), 0.27–1.97; P=0.53).

Limited evidence suggests that pasireotide therapy may be beneficial in preventing recurrent hypoglycemia due to insulinoma. Indeed, pasireotide LAR 40 mg/28 days significantly reduced hypoglycemic events in a patient with a G2 stage IV insulinoma who had undergone excision of the primary tumor and of liver metastases.
without achieving adequate glycemic control (Tirosh et al. 2016). Since both the pancreatic lesion and the liver metastases had a negative staining for SSTR5, the anti-hypoglycemic effect may come from inhibition of insulin secretion through SSTR5 activation on normal pancreatic beta-cells. Hendren et al. also described the case of a subject with malignant insulinoma and severe hypoglycemic episodes despite the use of diazoxide and octreotide LAR. Treatment with pasireotide LAR induced a near resolution of hypoglycemic events (Hendren et al. 2018). However, further investigation and, eventually, a phase III controlled trial for interventions would be needed to validate the use of pasireotide as a treatment in patients with advanced metastatic insulinoma and symptomatic hypoglycemia.

First-generation SSAs have demonstrated antitumor activity in patients with advanced well-differentiated NETs of the gastroenteropancreatic tract with or without secretory symptoms (Rinke et al. 2009, Caplin et al. 2014). Due to its wider binding profile, pasireotide should theoretically represent a more powerful antiproliferative agent; however, data supporting its role in tumor control for patients with NETs are still scarce. In patients with metastatic NETs of the digestive tract and carcinoid symptoms refractory to available SSAs at conventional doses, Wolin et al. found an improved, though not
statistically significant, tumor control rate at 6 months among patients receiving pasireotide LAR (60mg every 4 weeks) compared to the octreotide arm (40mg every 4 weeks) (62.7% vs 46.2%, OR 1.96; 95% CI, 0.89–4.32; \( P=0.09 \)). In a post hoc analysis, patients on pasireotide LAR had a 5-month longer progression-free survival (PFS) than patients on octreotide LAR (11.8 months vs 6.8 months), corresponding to a 54% reduction in estimated risk for disease progression or death (HR 0.46; 95% CI, 0.20–0.98; \( P=0.045 \)) (Wolin et al. 2015). Data from a small, open-label, phase II study (Cives et al. 2015) of pasireotide LAR (60mg every 4 weeks) have also shown promising antitumor efficacy with mean PFS of 11 months (95% CI, 7.6–16) in patients with locally unresectable or metastatic NET without prior systemic therapy, including octreotide or lanreotide. A greater effect was observed in patients with low-grade midgut carcinoids, low (<10%) hepatic tumor burden, normal baseline chromogranin A and high tumoral SSTR5 expression. When best response to therapy was evaluated using the RECIST criteria, 64% (18/28) of patients had at least stable disease with 13 patients showing some degree of tumor shrinkage. A recent phase I study evaluated the maximum tolerated dose and efficacy of pasireotide of long-acting pasireotide in patients with advanced NETs and documented disease progression. A total of 29 patients were treated with 80 mg (\( n=13 \)) and 120 mg/28 days (\( n=16 \)). Two partial responses were observed in the 16 patients receiving the 120 mg dose of pasireotide. Most patients (>75%) had stable disease treated with both doses. In addition, the median PFS (95% CI) was 8.3 months and 10.8 months in the 80-mg dose group and 120-mg dose group, respectively (Yao et al. 2017).

Long-acting intramuscular formulation of pasireotide is well tolerated as single therapy in patients with advanced NETs (Wolin et al. 2013). The safety profile of pasireotide includes gastrointestinal symptoms (such as nausea, diarrhea and abdominal pain) and fatigue, which are largely consistent with first-generation SSAs. However, compared with other SSAs, pasireotide therapy is associated with a higher frequency of hyperglycemia often requiring start/adjustment of antidiabetic drugs (Wolin et al. 2013). Increased fasting blood glucose is more evident in patients with a history of impaired fasting glucose or diabetes mellitus (Kvols et al. 2012). In a phase III study, hyperglycemia was observed in 15/53 (28.3%) and 3/42 (5.3%) patients treated with pasireotide LAR (60mg) and octreotide LAR (40mg) every 28 days, respectively. The rate of grade 3 or 4 hyperglycemia was higher with pasireotide LAR (9.4%) than with octreotide LAR (1.8%) (Wolin et al. 2013). Pasireotide-associated hyperglycemia seems to be mainly related to a marked suppression in insulin and incretins (GIP and GLP-1) secretion without any alteration in hepatic and peripheral insulin sensitivity. All five SSTR subtypes are variably expressed in human pancreatic islets, with a preferential expression of SSTR1 and 5 in beta-cells, and of SSTR2 in alpha-cells (Kumar et al. 1999). The different expression of SSTR2 and SSTR5 on pancreatic alpha- and beta-cells is probably the cause of a greater decrease of insulin secretion and lesser suppression of glucagon with pasireotide when compared to octreotide or lanreotide (Henry et al. 2013). A recent study defined the maximum tolerated dose for pasireotide LAR at 120mg/28 days; at this dose, a high incidence of bradycardia (31%) was observed (Yao et al. 2017).

**Pasireotide as a combined treatment in NETs**

The development and progression of NETs depend on the activity of complex signaling pathways which have been also described in other tumors (Walenkamp et al. 2014). Combination therapy represents a cornerstone of NET therapy, as a result of targeting several key pathways in a characteristically synergistic/additive manner. In addition, this approach potentially overcomes or delays the development of drug resistance. It has been reported that addition of SSAs to chemotherapy or biologic therapy may increase treatment efficacy (Wolin 2012). RADIANT-1 phase II trial reported a better median PFS in patients with pancreatic NETs treated with everolimus plus octreotide LAR (16.7 months) compared to that observed after everolimus alone (9.7 months) (Yao et al. 2010). On the basis of several preclinical and clinical trials, pasireotide may be effective not only as a single agent but also combined to standard or new compounds in the management of NETs (Fig. 1).

**Pasireotide plus everolimus**

Since several clinical trials together with *in vitro* and *in vivo* studies demonstrated the efficacy of targeting mTOR or SSTR in NET therapy, combined treatment with SSAs and everolimus has been considered as a potential therapeutic tool for NETs (Bousquet et al. 2012, Oberstein & Saif 2012). Surprisingly, a synergistic or additive *in vitro* inhibition of the PI3K/AKT/mTOR pathway through SSAs (octreotide and pasireotide) and everolimus combination was not always evident in NET cells, although each molecule independently suppressed this pathway. Indeed, there was...
not a favorable antitumor activity after incubation of NET cell lines (KRJ-I, P-STS, NCI-H727 and BON-1) with mTOR inhibitors and octreotide. This may be due to feedback mechanisms within the PI3K/AKT/mTOR pathway, such as the activation of AKT or cross-activation of tumor escape pathways (ERK/pERK) (Moreno et al. 2008, Svejda et al. 2011). Zatelli et al. showed that the combination pasireotide plus everolimus was unable to potentiate both antiproliferative and antiserectory effects of everolimus in primary cells from human bronchial carcinoid (Zatelli et al. 2010). Similar underwhelming results were reported for primary cultures of human pancreatic NETs. Everolimus plus pasireotide was not able to decrease either cell viability or chromogranin A secretion compared to single drugs. Interestingly, pasireotide alone induced apoptotic processes (through caspase activation), that were reverted by combined treatment, probably due to the activation of the survival pathways, such as AKT, induced by everolimus (Mohamed et al. 2017).

A phase I study evaluated the safety and feasibility of combining pasireotide and everolimus in 21 patients with locally unresectable or metastatic NETs of low (77%) or intermediate histological grade (23%). Patients were treated with escalating doses of pasireotide (600–1200 µg s.c. twice daily, followed by pasireotide LAR 40–60 mg i.m. monthly) and everolimus (5–10 mg daily). Hyperglycemia was one of the most commonly observed side effects (90% of cases), of grade 3 or 4 in 8 out of 21 patients. Other grade 3–4 side effects were uncommon (mucositis, diarrhea, rash, joint pain, prolonged QTc interval, hypophosphatemia, thrombocytopenia and leucopenia). In terms of efficacy, the best responses were stable disease in 19 patients (90%) and partial response in one patient (5%), evaluated according to RECIST criteria. No differences were observed according to primary tumor site (Chan et al. 2012).

COOPERATE-2 was a randomized phase II trial in which 160 patients with advanced, progressive grade 1–2 pancreatic NETs were treated with the combination of everolimus (10 mg daily) and pasireotide (60 mg/28 days) vs everolimus alone. The median PFS was similar in both arms, 16.8 months (12.1–19.6) in combination arm vs 16.6 months (11.1–19.5) in everolimus arm (HR 0.991 95% CI, 0.64–1.54), although partial response rate was significantly higher in combination arm (20%) compared to that with everolimus alone (6%). No difference in the overall survival was observed, with a median follow-up of 22.6 months. Higher incidence of hyperglycemia (all grades 76% vs 27%) and diabetes mellitus (26% vs 7%) was noted in the combination arm compared to everolimus alone, while rates of stomatitis, diarrhea, abdominal pain, pneumonitis and cardiac events were similar between both groups (Kulke et al. 2017). The combined treatment determined a higher grade of side effects, particularly for hyperglycemia, diarrhea and weight loss. The less favorable toxicity profile was responsible for a higher frequency of dose reduction and therapy discontinuation in patients treated with both compounds that may have an impact on PFS. Moreover, previous studies showed that, even though pasireotide binds with different affinity all the subtypes of SSA receptors, it exerts a different effect on SST2 internalization, as previously described (Mohamed et al. 2014). If this different mechanism exerts a role on pasireotide antitumor activity and tolerability, it should be better clarified.

A recent prospective, randomized and phase II trial study (LUNA trial) assessed the efficacy and safety of pasireotide (60 mg/28 days i.m.) and/or everolimus (10 mg daily) in 124 patients with unresectable or metastatic, well-differentiated lung (typical or atypical carcinoid) and thymus NETs. The analysis of relative change of tumor size from baseline showed 11/36 (31%) patients in the pasireotide group, 16/33 (49%) in the everolimus group and 24/33 (73%) in the combination group experienced some degree of tumor shrinkage, but only one patient in each group reached a partial response (2.4%). In the other cases, the tumor shrinkage was not a RECIST response. Median PFS was 8.5 months in the pasireotide group, 12.5 months in the everolimus group and 11.8 months in the combination group. The most common side effects reported during treatment with pasireotide (alone and in combination) were diarrhea, hyperglycemia and weight loss. Patients treated with everolimus (alone and in combination) experienced above all stomatitis and diarrhea. In combination group, there was a higher rate of adverse events, particularly for hyperglycemia, diarrhea, weight loss and asthenia (Ferolla et al. 2017).

**Pasireotide plus cabergoline**

Another potential target for the treatment of NETs is the dopaminergic system. SSTR and dopamine receptors type 2 (DR2) are frequently co-expressed in NETs and can heterodimerize, enhancing functional activity and exerting a synergistic inhibitory effect (Gatto & Hofland 2011). Since somatostatin and dopamine analogs could inhibit the secretion of several hormones, in particular IGF1 and IGF2 targeting indirectly IRA activation, van Adrichem et al. evaluated the possibility to combine SSAs plus cabergoline, a dopamine agonist, in human...
pancreatic NET cell lines (BON-1 and QGP-1). These cells highly expressed both IGF2 and IRA. IGF system has a tumor-promoting role and mitogenic effects in NETs and include IGF1, IGF2, IGF receptor (IGFR1 and 2), IGF-binding proteins, IRA and insulin receptor isoform B (IRB). In human pancreatic NET cell lines, pasireotide combined to cabergoline significantly decreased the IGF2 mRNA expression; no change on mRNA expression was observed during incubation with each compound alone or octreotide plus cabergoline. In addition, a stronger inhibition in IRA bioactivity has been observed with pasireotide plus cabergoline than each drug alone. These encouraging data showed that activation of SSTR2 and 5 together with DR2 could inhibit IRA activation induced by IGF2, and combined treatment with pasireotide and cabergoline could be an innovative approach to the treatment of NETs (van Adrichem et al. 2016). Interestingly, the heterodimerization property of these receptors has been recently used to develop several chimeric compounds that bound and synergistically activated both SSTR and DR2, showing significant antitumor effects, at least in vitro, in NETs (Culler 2011, Zitzmann et al. 2013).

Pasireotide plus teriflunomide

Among several signaling pathways involved in tumor progression, RAF1/mitogen-activated protein kinase kinase (MEK)/ERK1/2 pathway has an important role in the regulation of NET cell proliferation (Carter et al. 2013). Several in vitro studies in NET cells demonstrated that not only RAF and MEK inhibitors (Zitzmann et al. 2010, Iida et al. 2012) but also RAF1 activators (Cook et al. 2010, Fazio et al. 2014) showed antitumor effects in NETs. In addition, phosphorylation of ERK1/2 seemed to be important for the activity of SSAs, probably because of its role in the decrease of transcripts for Ki67 and in the induction of cell cycle arrest through p21 increase (Kidd et al. 2008). On the light of this evidence, Somnay et al. evaluated the antitumor activity of pasireotide in combination with teriflunomide, a Raf activator. The antiproliferative effect of pasireotide at low dose was improved by its association with teriflunomide in BON cells. Moreover, this combination was synergistic and able to induce a decrease in the expression of chromogranin A and ASCL1, both neuroendocrine biomarkers, and an increase of ERK1/2 phosphorylation. Finally, teriflunomide plus pasireotide increased the activity of proapoptotic enzymes, PARP and caspase-3, reducing at the same time the expression of some anti-apoptotic proteins (XIAP and Mcl-1) compared to either drug alone. These data demonstrated that combined therapy with these two drugs could represent a promising therapeutic option for NETs (Somnay et al. 2013).

Pasireotide plus aurora

Georgieva et al. proposed a new therapeutic approach to gastroenteropancreatic NETs using the aurora kinase B inhibitor, ZM447439, as antitumoral option in monotherapy or in combination with other standard chemotherapeutical drugs, including pasireotide. Unfortunately, pasireotide as a single agent showed a higher antiproliferative activity compared to combination with ZM447439 in BON cell line (Georgieva et al. 2010).

Ongoing clinical trials

Several other trials are currently investigating the role of pasireotide alone, or in combination with everolimus and/or loco-regional therapy in NETs. The objective of these studies is to clarify the efficacy of pasireotide in terms of safety, symptomatic and biochemical control, and effects on tumor mass and survival in NETs. We have found 8 ongoing clinical trials with this topic, listed at the www.clinicaltrial.gov website (Table 2).

A multi-institutional, prospective phase II open-label trial has the goal to clarify if pasireotide LAR 60 mg/28 days, as first-line therapy, can shrink or slow the growth of locally unresectable or metastatic carcinoid or pancreatic NETs. Patients with poorly differentiated neuroendocrine carcinomas or small-cell carcinomas and patients treated with prior systemic antineoplastic drugs, including SSAs, are excluded (NCT01253161, www.clinicaltrial.gov). Another phase II study is assessing the efficacy and safety of pasireotide in patients with rare tumors of neuroendocrine origin (Nelson syndrome, pancreatic NETs, pituitary and ectopic-ACTH secreting tumor), analyzing the number of patients attaining normalization or more than 50% reduction in primary biochemical tumor marker (NCT00958841, www.clinicaltrial.gov).

A phase II study is evaluating the effect of pasireotide on cortisol secretion in non-pituitary ectopic-ACTH secreting tumor. The purpose of this study is to investigate the efficacy of pasireotide (initial dose of 600 μg twice daily for one month, increased to 900 μg twice during the treatment period of 6 months) for normalizing 24-h urine-free cortisol in patients with ectopic ACTH-producing tumors. Salivary and plasmatic cortisol, clinical signs and symptoms and safety will also be evaluated (NCT02780882, www.clinicaltrial.gov).
A phase I study is currently evaluating the safety, pharmacokinetics and efficacy of pasireotide s.c. and LAR in patients with Merkel cell carcinoma, an aggressive neuroendocrine neoplasm of the skin (NCT01652547, www.clinicaltrial.gov).

The extension phase of COOPERATE-1 could provide more information about the toxicities and, as secondary endpoints, about efficacy of the combination of pasireotide and everolimus in the long term (NCT01590199, www.clinicaltrial.gov). Another phase I study is investigating the safety and activity of pasireotide, everolimus and hepatic selective internal radioembolization therapy in patients with pancreatic and intestinal NETs, with unresectable liver metastasis, of low-intermediate grade (NCT01469572, www.clinicaltrial.gov). Moreover, two studies are investigating for the first time the efficacy of the combination of everolimus and pasireotide in medullary thyroid cancer in terms of response rate and PFS (NCT01270321, NCT01625520, www.clinicaltrial.gov).

**Pasireotide as a combined treatment in non-endocrine tumors**

Beside NETs, SSTRs are aberrantly expressed in other tumors. Few preclinical and clinical studies evaluated the effects of pasireotide in combination with several drugs in non-endocrine tumors, suggesting a potential therapeutic use of these new combinations in NETs (Fig. 1).

**Table 2** Ongoing clinical trials in neuroendocrine tumors (NETs), as listed at the www.clinicaltrial.gov website, using pasireotide as search criteria.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Primary endpoint</th>
<th>Study ID</th>
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<tbody>
<tr>
<td>Study of pasireotide LAR in patients with metastatic NETs</td>
<td>Pasireotide</td>
<td>Phase 2</td>
<td>NETs</td>
<td>Progression-free survival</td>
<td>NCT01253161</td>
</tr>
<tr>
<td>An open-label, multicenter, single-arm study of pasireotide LAR in patients with rare tumors of neuroendocrine origin</td>
<td>Pasireotide</td>
<td>Phase 2</td>
<td>Pancreatic NETs, pituitary adenoma, Nelson syndrome, ectopic ACTH syndrome</td>
<td>Percentage of responders at month 6</td>
<td>NCT00958841</td>
</tr>
<tr>
<td>Open-label study to test the efficacy and safety of pasireotide in patients with ectopic ACTH-producing tumors</td>
<td>Pasireotide</td>
<td>Phase 2</td>
<td>Ectopic-ACTH secreting tumors</td>
<td>Normalization of 24h urine free cortisol</td>
<td>NCT02780882</td>
</tr>
<tr>
<td>A phase I of pasireotide s.c. followed by pasireotide LAR in patients with metastatic melanoma or metastatic Merkel cell carcinoma</td>
<td>Pasireotide</td>
<td>Phase 1</td>
<td>Metastatic melanoma, Merkel cell carcinoma</td>
<td>Safety and tolerability</td>
<td>NCT01652547</td>
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<tr>
<td>Extension Study to the COOPERATE-1 Study</td>
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<tr>
<td>Pasireotide, everolimus and selective internal radioembolization therapy for unresectable hepatic metastases</td>
<td>Pasireotide</td>
<td>Phase 1</td>
<td>NETs</td>
<td>Safety and tolerability</td>
<td>NCT01590199</td>
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<tr>
<td></td>
<td>Everolimus</td>
<td>Phase 1</td>
<td>NETs</td>
<td>Safety</td>
<td>NCT01469572</td>
</tr>
<tr>
<td>A 3-arm randomized phase II trial evaluating single agent and combined efficacy of pasireotide and everolimus in adult patients with radioiodine-refractory differentiated and medullary thyroid cancer</td>
<td>Pasireotide</td>
<td>Phase 2</td>
<td>Radioiodine-refractory differentiated thyroid cancer, medullary thyroid cancer</td>
<td>Response rate</td>
<td>NCT01270321</td>
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<td>SOM230 alone or in combination with RAD001 in patients with medullary thyroid cancer</td>
<td>Pasireotide</td>
<td>Phase 2</td>
<td>Medullary thyroid cancer</td>
<td>Progression-free survival</td>
<td>NCT01625520</td>
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<tr>
<td>Everolimus</td>
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Pasireotide plus chemotherapy

In several tumors, stromal cancer–associated fibroblasts (CAF) have a main role in cancer progression and in the development of chemoresistance via the secretion of growth factors and immune suppressive cytokines, mesenchymal–epithelial cell interactions and generation of specific niches within the tumor microenvironment that facilitate the acquisition of drug resistance (Wang et al. 2017). In pancreatic adenocarcinoma, pasireotide showed a significant antitumor activity through an effect on CAF (Moatassim-Billah et al. 2016). Exclusively, pasireotide, and not octreotide, was able to inhibit in vitro CAF tumorigenic features. CAF secretome, able to stimulate in vitro cancer cell survival, migration and invasive features, was abolished after incubation with pasireotide. This effect was mediated by the activation of SSTR1 and shutdown of the protein synthesis via 4E-BP1 in CAF. In mice orthotopically co-xenografted with the human pancreatic cancer MiaPaCa-2 cells and CAF, pasireotide was not able to inhibit tumor growth but abolished the formation of metastasis (Moatassim-Billah et al. 2016). In the light of these considerations and taking into account the implication of tumor microenvironment in chemoresistance, a promising pharmacological strategy has recently been suggested, combining pasireotide with gemcitabine, a chemotherapeutic drug used in the treatment of pancreatic adenocarcinoma. In nude mice xenografted with pancreatic cancer cells and CAF, gemcitabine and pasireotide decreased tumor growth with a dramatic increase in cancer cell apoptosis. The activation of SSTR1 by pasireotide on CAF inhibited the mTOR/4E-BP1 pathway and the secretion of chemoprotective and soluble growth factors, cytokines and/or chemokines, including interleukin 6 (IL 6), with a relevant role in the induction of chemoresistance (Duluc et al. 2015).

Combination of pasireotide and gemcitabine has manageable safety profile, as demonstrated in a phase 1 study enrolling patients with metastatic or locally advanced pancreatic adenocarcinoma. Patients were treated with gemcitabine 1000 mg/m² weekly, for 3 weeks every month and pasireotide LAR 40 or 60 mg every 28 days. Preliminary signals of activity were reported during this trial with a disease control rate of 68% (stable disease in 9/16 patients, partial response in 2/16 patients), with a median PFS of 4.1 months (range 1–16 months) and a median overall survival of 6.9 months (range 1–25 months) (Suleiman et al. 2015). Similar results were reported in a dose-escalation, open-label, phase 1 trial evaluating the combination of pasireotide and standard FOLFIRI (5-fluorouracil, leucovorin and irinotecan) regimen in 16 patients with advanced gastrointestinal malignancies. Treatment was well tolerated, 2 patients achieved partial response (colon cancer and esophageal cancer) and 7 patients had stable disease. Median PFS was 3.6 months (95% CI: 2.4–5.5 months) and median survival was 7.2 months (95% CI: 4.3–11.4 months) (Mahipal et al. 2015).

In the literature, there are no studies evaluating the effects of pasireotide on CAF in NETs. However, the relevant role of tumor microenvironment and the interplay between tumor cells and fibroblasts in the development and progression of NETs and probably in the induction of drug resistance is well known. In addition, in this tumor fibrotic complication (carcinoid heart disease, mesenteric/retroperitoneal fibrosis, etc.) may lead to devastating clinical sequela and affect prognosis (Laskaratos et al. 2017).

Pasireotide plus cyclooxygenase-2 inhibitors

The cyclooxygenase (COX) enzymes catalyze a key step in the synthesis of prostanoids, relevant mediator of inflammation and angiogenesis. COX-2 is overexpressed in cancer cells and is implicated in carcinogenesis, tumor progression and resistance to chemo- and radiotherapy. Somatostatin-14 inhibited COX-2 expression in colon cancer cells through SSTR3 and 5 activation and inhibited cell proliferation (Colucci et al. 2008). Interestingly, the combination of pasireotide and celecoxib, a selective COX-2 inhibitor, synergistically inhibited cell growth in hepatocellular carcinoma cells (HepG-2 cell line) through apoptosis induction (Xie et al. 2011). Furthermore, the combination treatment significantly prolonged survival of nude mice with HepG2 xenografts and down-regulated vascular endothelial growth factor expression (Xie et al. 2011). These results are potentially applicable in NETs. Indeed, several studies suggested a role of COX-2 in the pathogenesis and progression of NETs. COX-2 is expressed in pheochromocytoma tissue (Salmenkivi et al. 2001) and up-regulated in gastrointestinal and bronchopulmonary carcinoids (Mizuno et al. 2006). Moreover, COX-2 up-regulates both expression and bioactivity of chromogranin A in a cell line of rat pheochromocytoma (PC12) (Connolly et al. 2007). In a cohort of 247 patients with histologically confirmed primary or metastatic GEP-NET, COX-2 overexpression was found to be associated with poor differentiation, higher stage and lymphatic invasion and to be inversely correlated with
SSTR2 expression. Kaplan–Meier analyses also showed COX-2 overexpression being associated with poor overall survival (Kim et al. 2011). These data suggest that COX-2 could be a therapeutic target in a selected subset of NETs, with considerable potential for future therapy combining selective COX-2 inhibitors with pasireotide.

Conclusions and future perspectives

SSAs represent the cornerstone of therapy for patients with advanced G1-G2 NETs not eligible for surgery. Although a preliminary study supported a role of pasireotide in the therapy of patients with metastatic carcinoid syndrome refractory to conventional SSAs (Kvols et al. 2012), a phase III study showed that pasireotide LAR and high-dose octreotide LAR have similar efficacy for symptom control in patients with functional NET and symptoms inadequately controlled with the recommended doses of available SSAs (Wolin et al. 2015). In addition, it is still unknown whether pasireotide has greater antiproliferative effects than octreotide lanreotide, particularly in medically naive patients with NETs. After 6 months of treatment, a trend toward higher tumor control rate was observed with pasireotide LAR (60 mg every 4 weeks) in NETs, although it was statistically not significant (Wolin et al. 2015).

The efficacy of combination therapy with pasireotide plus everolimus in NETs is also controversial. Studies investigating the combination of pasireotide and everolimus showed a higher response rate, in terms of tumor stabilization and tumor regression, but this better response rate was not able to determine a statistically significant benefit in PFS compared to each drug alone.

A potential limitation in the majority of previous studies was the heterogeneous cohort of enrolled patients with unknown SSTR5 profile. This information could be relevant for the selection of patients responsive to pasireotide. Indeed, Cives et al. reported that high SSTR5 expression in NETs was associated with prolonged PFS in a small series of patients treated with pasireotide LAR (Cives et al. 2015). Therefore, the antitumor activity of pasireotide LAR warrants further exploration in adequately powered prospective phase III studies with symptom control, PFS and additional tumor control metrics as predefined endpoints and after a complete characterization of SSTR subtypes in NETs. This may identify subgroups of patients with greater rates of symptomatic, biochemical and radiological objective responses to pasireotide than to the currently available SSAs. Future trials should also investigate the potential effects of high-dose treatment with pasireotide in NETs. In fact, a phase I study with pasireotide at high dose (120 mg every 4 weeks) showed encouraging antitumor activity (Yao et al. 2017). Moreover, an association between pasireotide and other targeted therapy used in NETs, such as sunitinib or lenvatinib, should be explored. This treatment had a different toxicity profile from everolimus, and the association could be better tolerated.

In conclusion, without any evidence of a more potent antitumor effect and due to the less favorable toxicity profile of pasireotide, this drug is not currently used routinely as therapy in advanced NETs. However, we cannot exclude a role of pasireotide restricted to a subset of NETs with a specific SSTR profile. Recent preclinical studies demonstrated a potent antitumor activity of pasireotide in combination with dopamine agonists, Raf activators, chemotherapy and COX-2 inhibitors in several cancer models. Future studies will need to confirm these issues to improve the treatment of advanced NETs.

Declaration of interest

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