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Progress in the Formulation and Delivery of Somatostatin Analogues for Acromegaly

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Abstract

A 14-amino acid cystin bridge-containing neuropeptide was discovered in 1973 and designated as "*growth hormone-inhibiting hormone (GHIH),"* i.e. somatostatin. Its discovery led to the synthesis of three analogues which were licenced for the treatment of acromegaly: octreotide, lanreotide, and pasireotide. Somatostatin analogues are currently approved only as either subcutaneous (s.c.) or intramuscular (i.m.) long-acting injections. We examine the challenges that must be overcome to create oral formulations of somatostatin analogues and examine selected clinical trial data. While octreotide has low intestinal permeability, similar to almost all other peptides, it has an advantage of being more stable against intestinal peptidases. The development of new oral formulation strategies may eventually allow for the successful oral administration of potent somatostatin analogues with high therapeutic indices.

Key words: somatostatin, octreotide, oral peptide delivery, intestinal permeability, acromegaly

Acromegaly is a hormonal disorder arising from hypersecretion of both growth hormone (GH) and insulin-like growth factor I (IGF-I) as a consequence of a pituitary adenoma [1]. It is progressive, but is often only diagnosed after years of symptoms. The estimated incidence of acromegaly is between 0.2-1.1 cases/100,000 people/year [2], confirming it as an orphan disease by US and EU criteria. Patients with active acromegaly aggravate associated co-morbidities such as Type II *diabetes mellitus* and cardiovascular disease. Patients also suffer from physical deformities including coarsening facial feature and bony proliferation. Most of these complications are irreversible however, progression can be slowed once treatment starts. Excess GH in the body also interferes with production of other hormones produced by pituitary glands. In addition, vitamin and mineral homeostasis are also impacted by pituitary adenomas. These types of complications can be restored after initiation of therapy. With recent advances in the therapeutic options for treatment of acromegaly, most patients now achieve successful disease control. The treatment process typically includes transsphenoidal adenomectomy surgery, injections of somatostatin analogues alone or in combination with injections of the GH receptor antagonist, pegvisomant (Somavert®, Pfizer, USA) (Fig. 1) and possibly the dopamine agonist, cabergoline (Dostinex®, Pfizer, USA), as well as radiotherapy. At present, somatostatin analogues are considered to be the first-line therapeutic options for the majority of patients. To date, three somatostatin analogues, octreotide, lanreotide and pasireotide, have been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Despite good efficacy, the mode of administration for the analogues is limited to parenteral options: s.c. or i.m. injection. We examine the challenges that must be overcome in order to create successful oral formulations of somatostatin analogues and re-examine preclinical and clinical trial data, with emphasis on ia studies that have been conducted in order to to deliver octreotide orally. In addition, the role of metabolic enzymes and clearance pathways on the low oral bioavailability of somatostatin analogues is also discussed.

1. The pharmacology of somatostatin

Somatostatin is a native cyclic neuropeptide of 1638 Da molecular weight (MW) consisting of 14 amino acids [3]. It is widely distributed throughout both the central nervous system and peripheral tissues. It has a wide-ranging anti-secretory effect against GH, IGF, thyroid-stimulating hormone (TSH), insulin, and glucagon. It also inhibits tumour growth though

modulation of cell proliferation and angiogenesis [4]. Somatostatin exerts its inhibitory and anti-proliferative effect upon activation of somatostatin receptors (SSTs), of which five subtypes (1-5) have been identified to date. SSTs are G-protein-coupled receptors consisting of seven trans-membrane spanning domains. They are mainly expressed in central and peripheral nervous systems, endocrine organs and the gastrointestinal (GI) tract (Fig. 2A). Amongst the SSTs, SST2 and SST5 are the predominant subtypes expressed in the pituitary gland, the pancreas and thyroid gland [5,6]. Upon activation, each receptor recruits specific G proteins which lead to activation of second messengers. Suppression of hormone secretion is mediated by inhibition of adenylate cyclase leading to reduced levels of intracellular cyclic AMP, as well as the lowering of intracellular calcium mediated through the inhibition of calcium channels and the activation of potassium channels. However, activation of phosphotyrosine phosphatase by somatostatin plays a pivotal role in of the inhibition of cellular proliferation (Fig. 2B). Owing to the wide-ranging biological functions of native somatostatin, its possible therapeutic benefits have been studied. Unfortunately, the plasma half-life ($t_{½}$) of endogenous somatostatin is short (3 minutes) and this impeded clinical development [7]. This drawback spurred the development of stable potent analogues that could mimic the native molecule (Fig. 3).

2. Somatostatin analogues

Octreotide acetate (Sandostatin® and Sandostatin® LAR depot, Novartis, Geneva) and lanreotide (Somatuline® SR and Somatuline® autogel® depot, Ipsen Pharma, Paris) were the first-generation somatostatin analogues to be synthesized with much longer half-lives ($t_{½}$) than the native molecule [8,9]. The $t_{½}$ values of 2, 169, 108 and 600 hours were reported for Sandostatin®, Sandostatin® LAR, Somatuline® SR and Somatuline® autogel®, respectively [10–12]. Octreotide and lanreotide both have higher affinity than somatostatin for SST2 receptors, but have weak- and moderate affinity for SST3 and SST5 receptors, respectively. Pasireotide (marketed as Signifor® and Signifor® LAR, Novartis, Geneva) are second-generation analogues with $t_{½}$ values of 9.6 - 12.6 hours for the former and 375-443 hours for the latter. Pasireotide binds with high affinity to four out of five SSTs in the rank order of SST5> SST2> SST3> SST1 [13].

Sandostatin® was approved by the FDA in 1988, while its long-acting counterpart, Sandostatin® LAR was approved in 1998. Generic versions of Sandostatin® appeared from 2005 onwards. Octreotide acetate is a cyclic octapeptide of MW1019 Da that retains the essential receptor-activating motif of native somatostatin, Phe-Trp-Lys-Thr [14]. Compared to native somatostatin, octreotide is metabolically stable against intestinal peptidases, in part due to the presence of D-confirmation amino acids and the steric hindrance provided by a disulfide-bridge [15]. Octreotide is more efficacious in terms of its hormone anti-secretory effects than native somatostatin and is therefore suitable for the treatment of hyper-functional organ conditions including neuroendocrine tumours (NET) and acromegaly [4,16]. It is also used as a radioactive ligand in the diagnosis of neuroendocrine tumours [17]. The positron emission tomography (PET) tracer, ^{111}In-diethylenetriaminepentaacetic acid (DTPA)-octreotide (^{111}In-DTPA octreotide), was developed to probe SST receptors overexpressed on pituitary adenomas (Table 1) [18]. Targeting SST receptors on adenomas is important in the diagnosis and treatment of acromegaly. The pharmacology of octreotide has been extensively evaluated in patients with acromegaly. Clinical studies showed that octreotide induced significant but variable degree of adenoma shrinkage and that it normalized plasma IGF-1 levels, which in turn were dependent on adenoma SST2 expression [6,19]. Lanreotide (BIM-23014) became the second first-generation injectable octapeptide somatostatin analogue to be approved by the FDA as long-acting and depot formulations in 2007. It shows a comparable efficacy and safety biochemical profile to that of octreotide [11]. Both octreotide and lanreotide exert mild transient side-effects associated with long-term treatment. The most common side effects are related to the GI tract and these include nausea, diarrhoea and abdominal pain and bile stone formation [11,20].

Pasireotide (SOM230, Novartis) was designed to have a broader pattern of interaction with multiple SSTs [21,22]. Both the FDA and EMA approved pasireotide in 2014 as an alternative molecule for non-responders to the first generation analogues, as well as also for patients with acromegaly for whom surgery was not an option [23]. It is also used to control symptoms of the carcinoid syndrome associated with neuroendocrine tumours and it inhibits adrenocorticotropic hormone (ACTH) secretion in Cushing's disease [23]. The incidence and degree of hyperglycemia are higher in patients undergoing pasireotide treatment compared to those on first-generation analogues [16,24,25]. More studies are

required to further explore the precise mechanisms of pasireotide-mediated hyperglycemia [23]. Recently, Ipsen Pharma (Paris) developed a chimeric molecule, dopastatin (BIM-23A760) that has affinity for both SSRT and dopamine receptors [26]. Results from clinical trials in acromegaly however, provide evidence of relatively weak efficacy of dopastatin injections, so its further development as a therapeutic for management of acromegaly is uncertain [6,27].

3. Formulations of somatostatin analogues

During the five decades from the discovery of endogenous somatostatin and subsequent synthesis of analogues, a new era in the advanced treatment of acromegaly and other GH-related diseases resulted. Because octreotide has poor bioavailability after oral administration due to low permeability, its efficacy was detected upon i.v. or s.c. injection. Patients had a choice between the short-acting injectable immediate release formulation and the long-acting monthly formulation [28]. Sandostatin® was prepared as an acetate salt solution to be administered in the form of deep s.c. injections, two to three times daily. The recommended dose varies from 0.1 to 0.3 mg, although doses up to 3 mg/day may be necessary for symptom control [29]. The development of Sandostatin® LAR eliminated the need for daily injections and patients typically move to this monthly i.m. format within two weeks if they respond to initial s.c. injections of Sandostatin® according to the prescription information provided by Novartis:
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021008s018s019lbl.pdf)
Sandostatin® LAR is a depot in which the active substrate is encapsulated in biodegradable poly (lactide) co-glycolide (PLG) microspheres with surfactants (http://www.google.ie/patents/CA2501978A1). The recommended monthly dose of Sandostatin® LAR is up 30–60 mg [30]. In a non-blinded prospective multi-centre study 27 newly diagnosed patients with macro- or microadenomas were switched from Sandostatin® 100-200 µg three times daily (Phase A) to 20-30 mg every 4 weeks with Sandostatin® LAR for up to 6 months (Phase B). During Phase A, median serum GH levels were reduced from baseline by 80%, and there was a further reduction in mean GH levels after switching to Sandostatin® LAR in patients by 84% and 69%, respectively (28). The outcome demonstrated more symptomatic efficacy for the i.m.-administered analogue at three dose levels (10, 20, 30 mg) compared to the s.c.-administered version. In newly diagnosed patients its therefore

recommended to initiate therapy with Sandostatin® to determine the response and tolerance and then, upon achieving such outcomes, to then switch patients to Sandostatin® LAR [31].

There are several new octreotide formulations under clinical investigation and these include CAM2029 (Novartis) and DP1038 (Dauntless Pharmaceuticals, San Diego, USA) [32,33]. CAM2029 is based on FluidCrystal® technology (Camurus Pharma, Sweden), which is administered by the s.c. route once a month. Octreotide is suspended in a liquid matrix which permits the use of thin 22-27G needles. The depot formulation absorbs water from tissue after being s.c. injected resulting in *in situ* formation of a highly viscous liquid-crystal gel phase from which octreotide diffuses passively from the matrix at constant rate (Fig. 4). In a Phase I, randomized, open label study volunteers were injected with either Sandostatin® LAR or CAM2029 [34]. Compared with Sandostatin® LAR, CAM2029 showed a 4-5-fold greater bioavailability with more rapid and stronger suppression of IGF-1 in the 2 weeks after administration. The results from subsequent Phase 2 study also showed a well maintained control of disease symptoms in NET and acromegaly patient and a Phase III is planned [35]. Dauntless Pharmaceuticals, Inc. has recently announced positive results from a Phase I trial evaluating DP1038 in 12 healthy volunteers [36]. Dauntless's DP1038 is based on the proprietary Intravail® maltoside-based permeation enhancer technology of Aegis Therapeutics (San Diego, USA) for enhancing peptide absorption by the intranasal route [37]. Fig. 5 shows the progress of most octreotide formulations in development.

Ipsen introduced a short-acting lanreotide (Somatuline®) formulation to the clinic [11] which was followed by a sustained-release formulation (Somatuline® SR). Somatuline® SR was also based on a microparticle drug-delivery system and has a biphasic release profile [11]. Initial release occurs during the initial two days following administration when the peptide is released from the surface of a polylactide-co-glycolide (PLG)-based copolymer, followed by sustained release for 10-14 days. Several years later, Somatuline® autogel® was developed by Ipsen, based on self-aggregation properties of lanreotide. The autogel® is formulated as a low volume supersaturated solution of lanreotide acetate in pre-filled syringes for s.c. injection. A dose of 60, 90 or 120 mg every 28 days is recommended for treatment. Similar to Sandostatin® LAR, a significant reduction in tumour size of > 20% occurred in 75% of

patients with acromegaly who received Somatuline® autogel®. In addition, patients receiving monthly dosing of either Sandostatin® LAR or Somatuline® autogel® achieved similar acceptable plasma biomarker endpoints (i.e. GH < 2.5 µg/l and a normalized IGF-1), demonstrating that both formulations have equal efficacy [22,28,38]. Nevertheless, Somatuline® autogel® is typically preferred by patients over Sandostatin® LAR owing to its more convenient regime of administration: it is self- or care-giver injected and, unlike Sandostatin® LAR, does not require a medically-qualified person for administration [39]. Although the results from clinical trials over the past 30 years demonstrated efficacy of octreotide and lanreotide as first-line treatments for acromegaly, high numbers of patients with acromegaly remained non-responsive. Accordingly, the next-generation somatostatin, pasireotide (Signifor®, Novartis), was approved both the FDA and EMA as a second line therapy [23]. Recently, two formulations of pasireotide, one for s.c. administration (Signifor®), and a second long-acting formulation for i.m. injection (Signifor® LAR) have also been approved. Signifor® LAR is composed of microspheres of PLG containing pasireotide pamoate and exhibited an extended-release profile characterized by an initial burst release within 24 hours with plasma concentrations subsequently declining and then rising to a peak over 1 and 3 weeks, respectively [23,40]. A recent randomized double-blind trial evaluated in 385 treatment-naïve patients showed that Signifor® LAR gave favourable efficacy. In this scenario, Signifor® LAR therefore has emerged as an alternative treatment option for acromegaly alongside the first-generation somatostatin analogues. Table 2 summarises the various formulations of each analogue that have been approved.

4. Challenges for development of an oral formulation of somatostatin analogues

Patients with acromegaly experience low quality of life especially during the active stages of the disease [41]. A recent survey conducted in nine pituitary Centres across Germany, the UK, and the Netherlands highlighted factors that impact the lives of patients with acromegaly. Somatostatin analogues administered via monthly s.c. or i.m. injections were found to play a significant role in impairing patient quality of life and, according to the survey, a majority of participants stated that they would prefer an alternative non-injected route of administration [42]. However, non-injected administration for systemic delivery of somatostatin analogues has yet to be achieved. Nonetheless, new strategies may eventually allow for oral administration of potent analogues of somatostatin which also have high

therapeutic indices. The challenge for successful oral administration of peptides is usually due to a combination of poor permeability and metabolic instability in both the GI tract and the liver, ultimately resulting in low systemic bioavailability.

Stability against peptidases and intestinal permeability of octreotide have been assessed [15]. Octreotide is stable against GI enzymes because the most peptidase-vulnerable amino acid at position 4 in is in the stable D-conformation which makes it resistant [15]. Thus, the low bioavailability of octreotide is mostly caused by low small intestinal epithelial permeability (< 0.3%) [43]. Many groups have applied different strategies in order to improve oral absorption of octreotide however, most of these preclinical attempts failed to achieve therapeutic levels in plasma. Inclusion of permeation enhancers (PEs) in oral formulation of octreotide have been investigated. Several PEs that have a history of safe use in man are currently in preclinical trials to improve oral peptide delivery [44]. Drewe and co-workers found that absorption of octreotide in presence of the non-ionic detergent polyoxyethylene (24)-cholesterol-ether (POECE) was increased by 23 fold in rats and by 8 fold in man [43]. Use of bile salts as an enhancer of octreotide permeability was also evaluated by Sandoz Pharma. An oral formulation of 4 mg of octreotide was co-administered with either ursodeoxycholate (100 mg) or chenodeoxycholate (100 mg) to 10 healthy volunteers. Bioavailability was increased to 0.3% in the presence ursodeoxycholate and to 1.7% in the presence of chenodeoxycholate [45]. Several other permeation enhancers including carbohydrate-based systems and chitosan derivatives were also reported to yield promising results in preclinical studies, but none have been commercialized to date [46,47].

Another approach to enhance oral bioavailability of octreotide was based on the lipidic systems [48] and involved encapsulation in the aqueous core of liposomes [49]. A study by Parmentier et al. revealed a 4-fold increase in bioavailability in rats for a liposomal formulation containing 25% of a tetraether lipid [50]. An alternative strategy to deliver somatostatin analogues is to address first-pass metabolism and high clearance mechanisms. This strategy involves formulation of peptide with PEs as well as inhibitors of clearance. In addition to the role of drug metabolizing enzymes, transporters have an important role in regulating oral bioavailability and transport across barriers [51]. Several drug transporters

including ATP-dependent efflux transporters also known as the ABC (ATP-binding cassette) superfamily and uptake transporters from the SLC (solute linked-carrier) superfamily have been identified to play a role in intestinal uptake and hepatic distribution and elimination of octreotide [52–55]. Previous studies provided evidence that octreotide as both a substrate and inhibitor of P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2) [55,56]. The interaction of octreotide with the main hepatic drug transporters has also been recently investigated. One study suggested that octreotide acts as a potent inhibitor for OATP1B1 (organic anion transporting polypeptide) and to lesser extent for OATP1B3 and MRP2 and that it is also as a substrate for OATP1B1 [54]. The authors speculated that incidence of hyperbilirubinemia in some patients undergoing octreotide treatment might be due to inhibition of OATP1B1-mediating bilirubin clearance by octreotide. Less is known about the interaction of lanreotide and pasireotide with drug transporters, so the mechanism underlying the epithelial transport of these analogues needs to be investigated. Such knowledge would be of use in attempts ultimately to improve the pharmacokinetic properties of these peptides when administered by non-injected routes.

5. An oral octreotide formulation that completed Phase III: The Chiasma technology

Chiasma Pharma's (Jerusalem, Israel) Transient Permeability Enhancer (TPE®) technology is the one approach which led to the development of an oral octreotide acetate capsule for acromegaly that completed of Phase III trial [57]. This system involves formulating the peptide with enhancers including sodium caprylate in a water-in-oil suspension in order to increase intestinal absorption [16,58]. Preclinical studies illustrated the capacity of TPE® to open jejunal epithelial tight junctions in rats. The limitation in terms of the maximal molecule weight permeability (< 70 kDa) and duration of effect (1-2 hours) appears to minimize the risk of internalization of luminal pathogens, endo-bacterial toxins, lipopolysaccharide (LPS) or LPS fragments [58], however a firm conclusion can only be made in the event of repeat dose studies in man over extended periods as well as in post-marketing studies. In a Phase I study, a single dose of 20 mg octreotide capsule and 100 µg s.c. injection yielded comparable plasma concentration in 75 healthy volunteers. Suppression of plasma GH levels was observed after oral administration of a single dose of octreotide (declining from 1.3 ± 0.4 µg/l to 0.5 ± 0.2 µg/l). As the results from the Phase I study demonstrated adequate safety of oral octreotide (octreolin™), a Phase II study was

not formally conducted [59]. A collaboration between Roche (Geneva) and Chiasma resulted in scale-up of the Octreolin™ production for Phase III. In 2014 however, Roche (Geneva) pulled out of their collaboration with Chiasma to develop Octreolin™ following the initial part of the Phase III study (http://www.globes.co.il/en/article-roche-cancels-600m-chiasma-deal-1000961276). Subsequently Chiasma moved to the second part of Phase III independently and re-branded the formulation as oral octreotide capsules (Mycapssa™).The outcome from the Phase III baseline-controlled open-label, multi-centre clinical trial involving 155 patients administered Mycapssa™ showed maintenance of biochemical responses in 65% of patients at the end of the initial trial period (7 months) and in 62% at the end of an extension study for responders lasting a total duration of 13 months [16,60]. Recently, Biermasz et al., summarized all the preclinical, Phase I and Phase III clinical trials on oral octreotide [61]. Despite a Complete Response Letter from the FDA for Chiasma's oral octreotide New Drug Application (NDA) application in 2016, the company is currently conducting an additional Phase III clinical trial (MPOWERED^{TM} (NCT02685709) in the hope of achieving marketing authorization from the EMA.

An alternative and more radical approach for oral octreotide delivery might be to eventually physically deliver it across to the small intestine by means of a microneedle-based intestinal delivery system. Recently, two partnerships between Rani Therapeutics (San Jose, CA, USA), and both Novartis and MedImmune (Gaithersburg, NJ, USA, a subsidiary of Astra-Zeneca (Molndal, Sweden)) were initiated to capitalize on Rani's "robotic pill" to deliver biologics. When the pills dissolves, a spring-loaded mechanism is signalled to push sugar-based micro-needles through the outer layer of the capsule, delivering the protein through the intestinal wall (http://www.ranitherapeutics.com/). In addition, researchers from Massachusetts Institute of Technology (MIT) have recently described capsule designs based on a different microneedle approach in which capsules were coated with stainless steel microneedles rather than sugar needles. After digestion, the capsule injects drugs directly into the lining of intestinal wall; the concept has been tested in a pilot study in swine [62], but the major challenge is still likely to be questions concerning possible toxicity in terms of intestinal blockage or the fate of the microneedles.

6. Market overview for treatment of acromegaly

According to a recent Global Data Opportunity Analyzer Report [63], by the end of 2018 the acromegaly and gigantism treatment market is forecasted to grow to $707m at a Compound Annual Growth Rate (CAGR) of 3.74% over the five-year period across US and 5 European Union countries (France, Germany, Italy, Spain and UK). The US market generated $382m in 2013 and is forecasted to grow to $478m by 2018 at a CAGR of 4.58%. The EU market is expected to grow from $209m to reach sells of $229m in 2018. The acceptability of newer formulations of existing drugs, increased use of easy to use prefilled injection devices and expected launches of novel drug molecules in major therapy areas will contribute to the growth in the sells market in the forecast period (2013-2018) [63]. Both Novartis's Sandostatin® and Sandostatin® LAR dominate the market despite patent expiration in 2014 in the US. So far, there is no generic competition. In 2016, Novartis made a profit of $853m on its two formulations and, according to EvaluatePharma, that profit will rise slightly in 2017 and 2018 (http://www.fiercepharma.com/special-report/5-sandostatin-lar). The recent launch of Signifor® LAR (Novartis) is expected to yield initial annual sales of $63m. In the event that an oral octreotide is eventually approved, annual sales are estimated at $28m.

7. Conclusion and future perspective

Successful surgery and medical treatment with somatostatin analogues improves co-morbidities and quality of life in the majority of patients with acromegaly. However, the various analogues that have been evaluated over recent decades are still only available as parental formulations. Oral methods for peptide delivery may create a formulation for those who cannot tolerate monthly injections, a niche product. Further studies are required to explore the best approach to improving oral bioavailability of somatostatin analogues including investigating the interplay between enhanced intestinal absorption and hepatic predisposition. Deeper understanding of molecular structure, function, signalling pathways and possible genetic polymorphism associated with somatostatin receptors will help enormously in the proper selection of somatostatin analogues. Finally, as we are now experiencing an era of personalized medicine, establishing new and suitable biomarkers for the currently-available somatostatin analogues will represent a major advance in shifting from trial and error to a more precise personalized therapeutic selection [23,38,61,64].

Executive summary

- Acromegaly is a consequence of chronic production of both growth hormone (GH) and insulin-like growth factor I (IGF-I), attributed in the majority of cases to pituitary adenoma and occurring with a population prevalence 0.2-1.1 cases/100,000 people/year.
- The first somatostatin analogue, octreotide, was identified over 30 years ago, followed by potent analogues including lanreotide and pasireotide. These analogues of native somatostatin are the foremost therapies for patients with acromegaly.
- Despite efforts to deliver oral analogues, no non-injected administration route formulations for systemic delivery of somatostatin analogues have been approved by the FDA or EMA.
- There are several strategies to further improve oral formulation of the somatostatin analogues, particularly for octreotide. Drug-device combination designs such as intestinal microneedles and intestinal patches are promising alternatives to more traditional formulation approaches built around permeation enhancers in emulsion-based systems.

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Figures

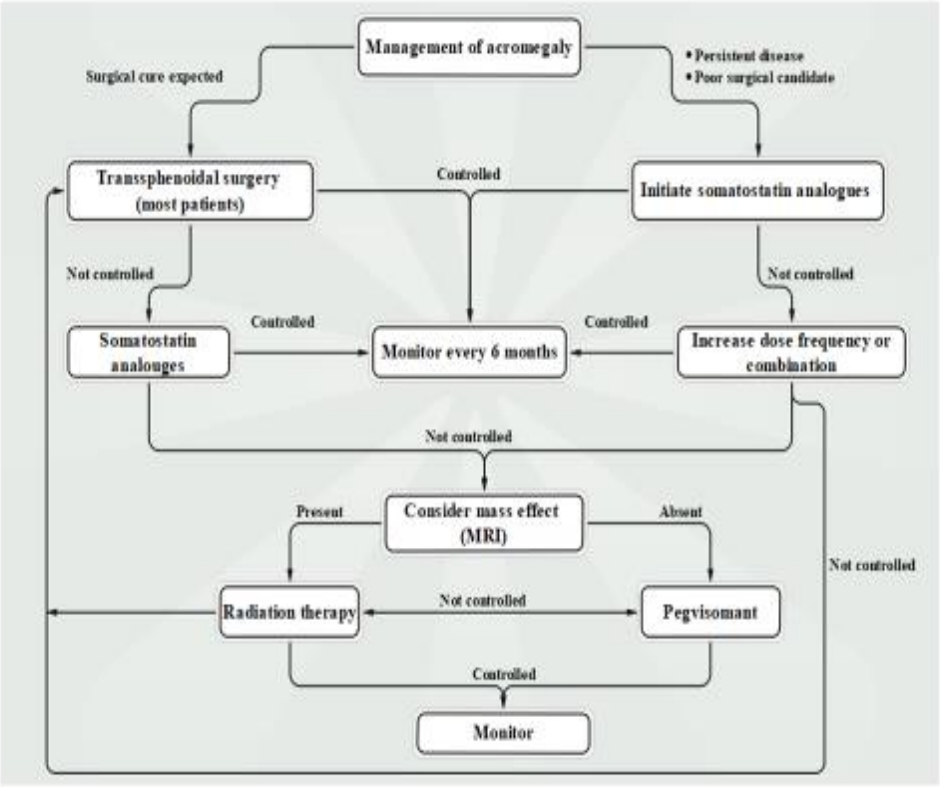

Fig. 1

Fig. 1. Treatment strategy for the patient with acromegaly. This management refers to the patient with GH-secreting pituitary adenoma. Adapted with permission fromSpringer Ltd [28]. Copyright [2009]).

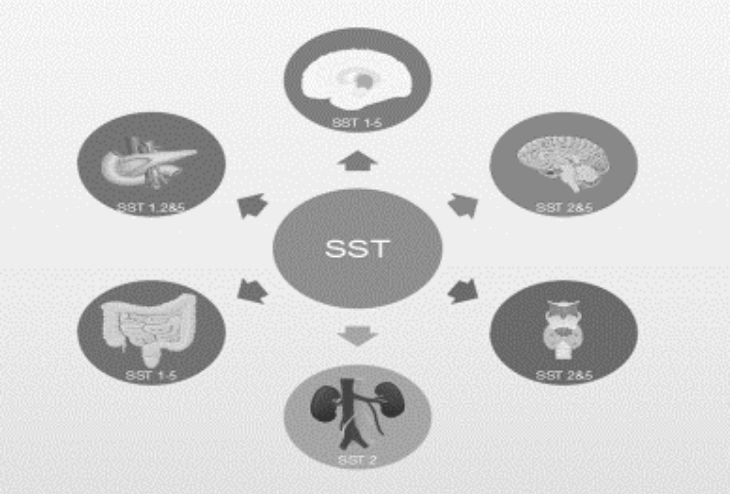

Fig. 2. A. Tissue distribution of somatostatin receptors (SST 1-5).

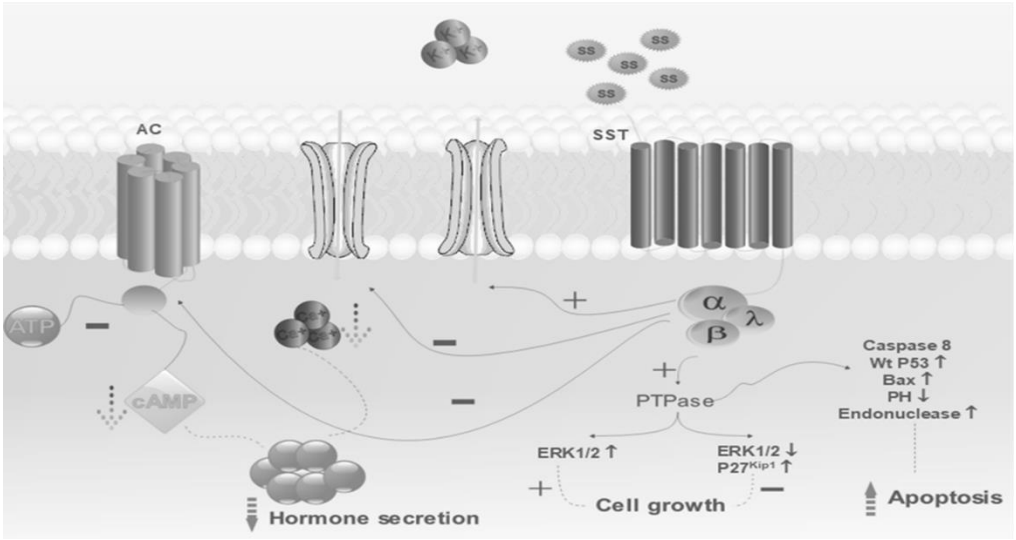

Fig. 2 B. Diagram of somatostatin receptor signaling in pituitary adenoma. Somatostatin (SS) binds to G-protein-coupled receptor (SST) that regulates various intracellular proteins leading to reduced hormone secretion. Inhibition of hormone secretion is mediated by inhibition of adenyl cyclase (AC) and Ca^{+}-channels with a subsequent fall in intracellular cyclic adenosine monophosphate (cAMP) and intracellular Ca^{+}. SS also activates phosphotyrosine phosphatases (PTPase) which regulates different intracellular second messengers and pathways including ERK, extracellular signal regulated kinase; $P27^{Kip1}$, cyclic-dependent kinease inhibitor 1B; Wt P53, wildtype P53; PH_i, intracellular PH and Bax, BCL-associated X protein, leading inhibition of growth and induction of apoptosis (Fig. 2B is adapted with permission from Springer Ltd. [38]. Copyright [2017]).

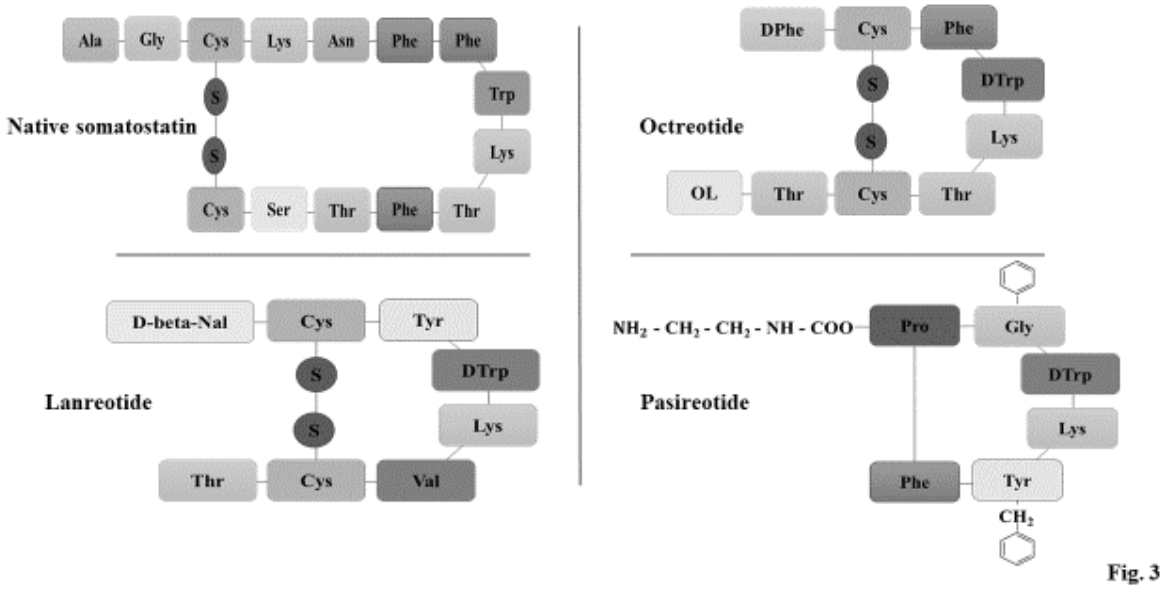

Fig. 3. The structure of native somatostatin and somatostatin analogues: octreotide, lanreotide and pasireotide. Abbreviation: Ala, Alanine; Asn, Asparagine; Cys, Cysteine; Gly, Glycine; Lys, Lysine, Nal, Naphthylalanine; Phe, Phenylalanine; Pro, Proline; Ser, Serine; Thr, Threonine; Trp, Tryptophan; Tyr, Tyrosine; Val, Valine.

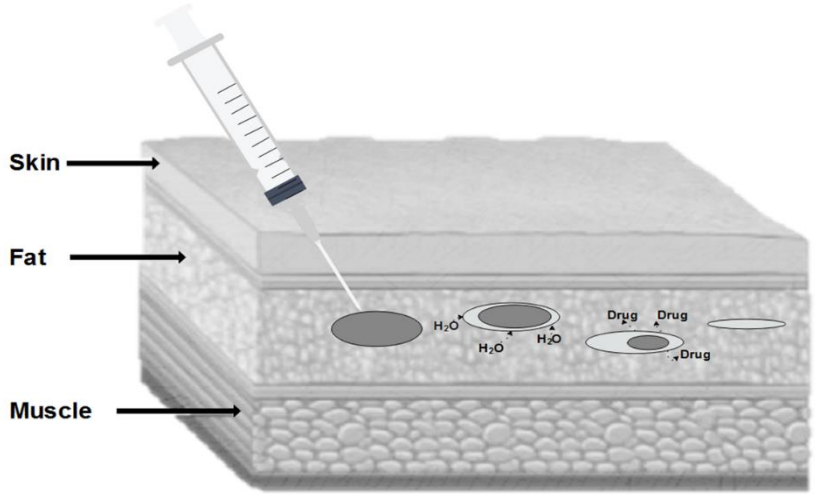

Fig. 4: A. simplified representation of Camarus's (Lund, Sweden) FluidCrystal® technology. The subcutaneous (s.c.) depot comprises a lipid-based formulation that is easy-to-use using conventional needles. After s.c. injection, the formulation absorbs water leading to liquid crystal gel formation (1) followed by biodegradation of depot (2) and release of the active substrate from the matrix (3).

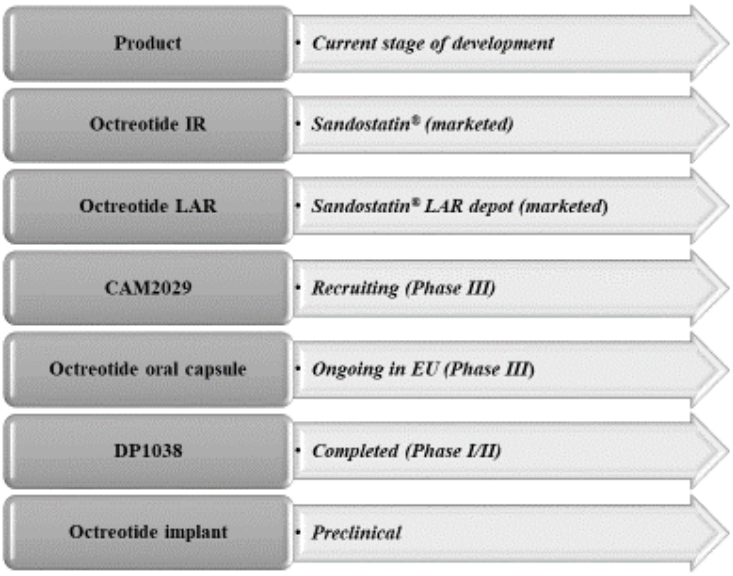

Fig. 5. Pipeline of octreotide formulations.

Table 1: Somatostatin receptor (SST) subtype expression in human pituitary adenomas (adapted with permission from Elsevier Ltd [65]. Copyright: [2017]).

Somatostatin receptor subtype				
SST1	SST2	SST3	SST4	SST5
59%	92%	67%	6%	89%

[*] *Percentile of tumours expression SST based on solution hybridization, ribonuclease protection assay, RT- PCR, qRT PCR, in situ hybridization and immunohistochemistry.*

Table 2: Somatostatin analogous currently marketed or in clinical trials

Trade name	Active	Receptor-affinity	Dose level and format	Route	Recommended Dose/frequency	Status	Manufacturer
Sandostatin®	Octreotide acetate	SSTR2; SSTR5	0.05,0.1 and 0.5 mg in l ml Multi-dose vial: 1mg in 5 ml	Deep s.c. injection i.v. infusion	0.05-0.1 mg every 8-12 hours	Approved by FDA and EMA for acromegaly	Novartis
Sandostatin® LAR depot	Octreotide acetate	SSTR2; SSTR5	10, 20 and 30 mg Powder for injection	i.m. in the gluteal region	10-30 mg every 28 days	Approved by FDA and EMA for acromegaly and neuroendocrine tumours	Novartis
	Octreotide acetate	SSTR2; SSTR5				Phase III completed; not approved by FDA; new application scheduled for EMA	Chiasma
Octreotide hydrogel	Octreotide	SSTR2; SSTR5	84 mg	s.c. implant		Study terminated	Endo Pharmaceuticals
	Octreotide acetate	SSTR2; SSTR5		Intranasal administration (Intravail® technology		Phase I	Dauntless Pharmaceuticals

				Aegis Therapeutics)			
	Octreotide chloride	SSTR2; SSTR5	Expected 10 and 20 mg Ready-to-use	s.c. injection (FluidCrystal® technology from Camurus)		Phase III	Novartis
Somatuline® LA	Lanreotide acetate	SSTR2; SSTR5	30 mg Powder for injection	i.m. injection	30 mg every 7-14 days	Approved by FDA and EMA for acromegaly and neuroendocrine tumours	Ipsen Pharma
Somatuline® Autogel® depot	Lanreotide acetate	SSTR2; SSTR5	60, 90 and 120 mg Prefilled syringe	Deep S.c. injection	60-120 mg every 28- 56 days	Approved by FDA and EMA for acromegaly and neuroendocrine tumours	Ipsen Pharma
SIGNIFOR® LAR	Pasireotide pamoate	SSTR1-3; SSTR5	20, 40 and 60 mg Powder for injection	i.m. injection	40 mg every 28 days	Approved by FDA and EMA for acromegaly	Novartis
	Dopastatin	SSRT2, SSRT5, Dopamine 2		s.c. injection		In clinical trial	Ipsen Pharma