Chapter 19
Perspectives on Combination Medical Therapy in the Treatment of Acromegaly

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Introduction

The goals of acromegaly treatment include insulin-like growth factor-1 (IGF-1) normalization, reduction in growth hormone (GH) levels (to <1.0 μg/L), decrease in tumor volume, and improvement in clinical symptoms [1–4]. Surgical pituitary tumor removal is the first-line treatment of choice. However, GH excess remains uncontrolled in 15–20% of patients who have microadenomas and is as high as 60% in patients with a macroadenomas [5, 6]. Medical therapy is indicated for persistent disease after surgery. Radiotherapy is usually reserved as a third-line treatment option in patients who have persistent disease or tumor growth despite surgery or medical therapy [1].

Somatostatin receptor ligands (SRLs) are the cornerstone of medical therapy [1]. However, as monotherapy, SRLs achieve IGF-1 normalization in only approximately 17–35% of unselected cases [7–9], with no differences in efficacy between the two first-generation, long-acting release (LAR) preparations, octreotide (OCT), and lanreotide (LAN) autogel (ATG) [10]. These SRLs have highest affinity to somatostatin receptor subtype 2 (SSTR2). When used as adjunct therapy after surgery, tumor volume reduction is observed in 30–40% of cases [11]. Several tumor characteristics, including sparsely granulated somatotroph adenomas [12, 13], a lack of somatostatin receptor (SSTR) expression [12], and high Ki67, have been shown to predict SRL resistance, affecting approximately 10% of acromegaly patients [14].

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Pasireotide LAR (PAS) is a multireceptor-targeting SRL with higher affinity to SSTR5 compared to SSTR2, SSTR3, and SSTR1. Approximately 20% of patients who are resistant to maximum doses of OCT LAR or LAN ATG achieve biochemical control with PAS [15, 16]. As such PAS is an option for patients who do not respond to first-generation SRLs [17]. The GH receptor antagonist, pegvisomant (PEG), and the dopamine agonist (DA), cabergoline, may also be used as monotherapy. Pegvisomant clinical trial data suggests disease control is achieved in more than 90% of patients with daily subcutaneous (s.c.) PEG injections. However, in longer-term "real-life" studies, IGF-1 normalization is observed in 75% of patients at 2 years and in two thirds at 5 years [18–20]. Results of a recent meta-analysis are consistent with disease control in 72% (64–78.4% [95% confidence interval; CI]) of patients [21]. Conversely, due to a modest effect, cabergoline is considered mainly in patients with mildly elevated IGF-1 (levels up to two times above the upper limit of normal; ULN) [1, 17, 22].

Combination medical therapy is therefore an approach that should be considered when managing those patients who are inadequately controlled after surgery and who are poor SRL monotherapy responders [23, 24]. Additive and possibly synergistic mechanisms are the aim of a combined medical treatment strategy. Results include improved efficacy, while minimizing individual medication side effects, potential dose decreases and/or less frequent s.c. injections, and thereby reduced cost. Combination therapy has also been suggested to be efficacious in selected elderly acromegaly patients [25].

Somatostatin Receptor Ligand and Dopamine Agonist Combination Treatment

Dopamine-2 receptor (D2R) is expressed on both somatomammotroph and pure GH-secreting adenomas and DAs suppress GH secretion in acromegaly. Of the two commercially available DAs, only cabergoline is considered an acromegaly medical treatment as bromocriptine normalizes IGF-1 in only 10% of cases [26]. In contrast, based on a 2011 meta-analysis of five studies, cabergoline monotherapy normalizes IGF-1 in 34% of patients [22]. Greater efficacy was observed in patients with mild IGF-1 elevations, <1.5 times above the ULN.

Several small studies undertaken between the years of 2000 and 2010 demonstrated a beneficial effect of adding cabergoline to SRL treatment in patients with persistent GH excess while on SRL monotherapy [27–31]. Normalization of IGF-1 was observed in 42–56% of patients. Similarly, in the aforementioned meta-analysis, based on individual data derived from 77 patients, IGF-1 normalization was observed in more than half of patients, with a 30% reduction in IGF-1 after 6 months. The addition of cabergoline resulted in a further 22% reduction in IGF-1 beyond that attributable to SRL monotherapy [22]. Similar to monotherapy, a lower baseline IGF-1 was the best predictor of efficacy. Cabergoline doses required in the treatment of acromegaly are, however, two to five times higher (mean 2.5 mg/week) than the usual recommended dose for hyperprolactinemia (0.5–1.0 mg/week).

Some retrospective observational studies have demonstrated more conservative IGF-1 normalization rates of 25–48% with SRL-cabergoline combination therapy [32–34]. Data from prospective studies also suggest lower efficacy rates of between 30 and 40%. In a study by Mattar et al. [35], IGF-1 normalized in 7 of 19 patients (37%) when cabergoline was added, at a maximum dose of 3.5 mg/week, to OCT LAR treatment, with effects persisting at 18 months (range 12–27 months). In another prospective study, Vilar et al. [36] demonstrated IGF-1 normalization in 21 of 52 patients (40.4%) at 6 months, which was sustained at 12 months. Mean cabergoline dose required was 2.2 mg/week, with some patients requiring up to 3 mg/week. Similar to previous studies, a lower baseline IGF-1 of up to 2.2-fold above the ULN was associated with better outcomes.

There is limited data related to tumor volume reduction in patients who are on a combined SRL-cabergoline treatment, and mechanisms resulting in GH suppression are unclear. Baseline prolactin levels, positive immunohistochemical staining for prolactin, and D2R expression have not been shown to predict treatment efficacy [34–36]. Importantly, the efficacy of cabergoline appears to wane with time [37]. This phenomenon was recently highlighted in a large retrospective single-center study of patients treated with cabergoline either as monotherapy or in combination with SRLs. At a median of 34 months (range 3–88 months), disease control was demonstrated in 20/62 patients (32%) on combination therapy with cabergoline (median 2.5 mg/week, range 1.5–2.5 mg/week) and SRLs. However, treatment escape was seen in in six patients (30%) after 38 months (range 10–55 months). Overall, long-term disease control was only observed in 23% at 60 months (range 20–88 months) [38]. Interestingly, in this study, pre-treatment GH, but not IGF-1 levels, predicted response to combination treatment.

Results of a combination study that evaluates oral octreotide capsule (OOC) and cabergoline are published (https://clinicaltrials.gov/ct2/show/NCT02685709) [39, 40]. This is a phase 3, randomized open-label study of patients well controlled on injectable SRLs, who switch to OOC. The study will assess in a sub-analysis, the effectiveness OOC-cabergoline combination in those with inadequate biochemical control on OOC alone in the run-in phase. If successful, this will represent the first available oral combination therapy that may be suitable for some patients.

The synergistic effect of SRLs and DAs has also led to the development of chimeric compounds that bind to both D2R and SSTRs, particularly SSTR2 and SSTR5. A chimeric compound BIM-23A760 was found to suppress GH more effectively than OCT, cabergoline, or the SRL-cabergoline combination, when used in vitro. Further studies, however, demonstrated that it produced interfering metabolites that compete with intrinsic drug activity, resulting in decreased efficacy with repeated injections [41, 42]. Another chimeric compound, BIM-065, has greater potency and efficacy and lacks interfering metabolites. In in vitro studies, BIM-065 has been found to decrease GH secretion and decrease cell viability in GH-secreting adenomas, via increased apoptosis [43]. Further studies in acromegaly patients are needed, but this novel compound may prove to be a promising new option for acromegaly treatment.

Adverse Effects

Adverse effects that are most commonly reported for SRL-cabergoline combination therapy include nausea, headache, postural hypotension, and dizziness. Despite high doses of cabergoline used to treat acromegaly and an inherently increased risk of valvular disease with GH excess, no association has been found between the use of cabergoline and the development of clinically relevant cardiac valve disease (CRVD). In a large cross-sectional and a 4-year longitudinal study, compared to acromegalic controls, patients who received cabergoline did not have a higher prevalence or incidence of valvular regurgitation [44]. Valvular abnormalities seem to be more likely related to acromegaly disease itself than to cabergoline use [2, 45].

Somatostatin Receptor Ligand and Growth Hormone Receptor Antagonist Combined Treatment

Greater efficacy has been reported with a SRL-PEG than a SRL-DA combined treatment therapy, likely owing to the direct effect of GH receptor antagonism in blocking peripheral IGF-1 production. The newest addition to the armamentarium of treatment options is the combination of PAS and PEG. First-generation SRL-PEG and PAS-PEG studies are highlighted in Table 19.1.

Long-Acting First-Generation Somatostatin Receptor Ligands and Pegvisomant (SRL-PEG)

Primary Efficacy Endpoints

In patients with acromegaly who are inadequately controlled with high-dose long-acting SRLs, the addition of PEG at a median once-weekly dose of 60 mg (range 40–80 mg) was first reported in 2005 to normalize IGF-1 at any point in 95% of patients [46]. Subsequently, in one of the largest studies to date, Neggers et al. [47] reported the outcome of 141 patients (mean IGF-1 1.9 × ULN) who had PEG added to SRL their treatment regime and were treated for a median of 4.9 years. Normalization of IGF-1 at any point was observed in 97% of patients with the addition of a median weekly PEG dose of 80 mg (range 60–120 mg). Treatment outcomes were similar in patients who had undergone surgery and in those patients receiving primary medical therapy.

Other multicenter studies, however, have reported lower efficacy rates of 60% at 6–12 months. Van de Lely et al. [48] reported IGF-1 normalization in 79% at any point in the study, but 58% at the 28-week study ended with PEG-LAN. Similarly, in a prospective randomized controlled trial, Trainer et al. [49] demonstrated that

Table 19.1 First-generation somatostatin receptor ligand (SRL)-pegvisomant (PEG) and pasireotide LAR (PAS)-PEG combination studies (adapted from Lim and Fleseriu [24])

Study (year) (patient *n*)	Study design	Prior SRL treatment at time of enrollment	Treatment groups	Study treatments		Insulin-like growth factor-1 normalization[a] (%)		Median weekly effective PEG dose (mg)	Tumor size	Glycemic control	QoL/ symptom improvement	>Threefold elevation in hepatic enzyme with SRL-PEG (%)
				SRL	Pegvisomant	At any time	At study end					
Somatostatin receptor ligand-Pegvisomant add on therapy studies												
Feenstra (2005) (26)	Prospective, OL Duration: 42 weeks Objective: dose-finding, efficacy	≥ 6 months inadequate control	SRL-PEG	LAN 120 mg/ month or OCT 30 mg/ month	Starting dose: 25 mg/week (adjusted q6 weeks until IGF-1 is normal) Maximum dose: 80 mg/week	95	NA	60 (40–80)	No tumor growth seen in all 19 patients with available MRIs	NA	NA	19.2
Neggers (2007) (32)	Prospective, OL Duration: median 138 weeks (range: 35–149) Objective: efficacy and safety	≥ 6 months inadequate control	SRL-PEG	LAN 120 mg/ month or OCT 30 mg/ month	Starting dose: 40 mg/week (adjusted q6weeks until IGF-1 is normal) *Dose reduced if IGF-1 level falls in the lowest quartile* Maximum dose: 160 mg/week	100	NA	60 (range: 40–160)	>25% decrease in 13%[b] No change in size in the remaining	9/10 patients with DM had significant HbA1c decrease that continued after IGF-1 stabilized	Yes	15.6

(continued)

Table 19.1 (continued)

Study (year) (patient *n*)	Study design	Prior SRL treatment at time of enrollment	Treatment groups	Study treatments		Insulin-like growth factor-1 normalization[a] (%)		Median weekly effective PEG dose (mg)	Tumor size	Glycemic control	QoL/ symptom improvement	>Threefold elevation in hepatic enzyme with SRL-PEG (%)
				SRL	Pegvisomant	At any time	At study end					
Neggers (2009) (86)	Prospective, OL Duration: up to 4.5 years Objective: safety	≥ 6 months inadequate control (*n* = 63)	SRL-PEG	LAN 120 mg/ month or OCT 30 mg/ month	Starting dose 25 mg/week (*n* = 19) 40 mg/week (*n* = 13) Variable starting dose guided by baseline IGF-1 (*n* = 26)	NA	NA	NA	≥20% decrease in 19%[c] No increase in any patients	NA	NA	15.1
		Controlled on SRL monotherapy (*n* = 23)			PEG added for QoL Starting dose: 20 mg/week Median dose: 60 mg/week							
van der Lely (2011) (57)	Prospective, OL Duration: up to 28 weeks Objective: efficacy and QoL improvement	≥ 6 months inadequate control[d] (confirmed on a 4-month run-in period)	SRL-PEG	LAN 120 mg/ month	Starting dose: 60 mg/week (adjusted q8weeks until IGF-1 is normal) Maximum dose: 120 mg/week	78.9	57.9	60[e]	>20% decrease in 13.2% >20% increase in 24.5%	Decrease in mean fasting insulin in nondiabetic patients after combination	Yes	11[f]

Neggers (2014) (141)	Prospective, OL Duration: Median 4.9 years (0.5–9.2 years) Objective: long-term efficacy and safety	≥ 6 months inadequate control (n = 112)	SRL-PEG	LAN 120 mg/month or OCT 30 mg/month	Starting dose 25 mg/week (n = 27) 40 mg/week (n = 18) Variable starting dose guided by baseline IGF-1 (n = 67) (adjusted q6–8 weeks until IGF-1 is normal)	97.3	NA	80 (range: 60–120)	≥20% decrease in 16.9%[g] Significant tumor growth In 1 patient who required TSS, followed by RT	NA	NA	15.6
		Controlled on SRL monotherapy (n = 29)			PEG added for QoL Starting dose: 20 mg/week Median dose: 60 mg/week							
Somatostatin receptor ligand-pegvisomant or pasireotide-pegvisomant vs monotherapy comparison studies												
Trainer (2009) (84)	Prospective, OL, randomized Duration: up to 40 weeks Objective: efficacy and safety	≥ 6 months inadequate control	PEG-SRL (n = 29)	OCT varying doses (median 30 mg/month)	Starting dose: 10 mg/day (adjusted in 5mg increments q8weeks until IGF-1 normal) Maximum dose: 30 mg/day Minimum dose: 5 mg/day	73	62	105	≥20% increase in 1 patient on PEG monotherapy	Mean fasting and post-OGTT glucose an HbA1c significantly Lower only in monotherapy group No change in combo group	Yes, in both groups	13.8[h]
		≥ 6 months inadequate control	PEG monotherapy (n = 27)	–		60 (ns)[i]	58 (ns)	140				
		Controlled on SRL monotherapy	SRL monotherapy (n = 28)	OCT varying doses (median 20 mg/month)	–	–		NA				

(continued)

Table 19.1 (continued)

Study (year) (patient *n*)	Study design	Prior SRL treatment at time of enrollment	Treatment groups	Study treatments		Insulin-like growth factor-1 normalization[a] (%)		Median weekly effective PEG dose (mg)	Tumor size	Glycemic control	QoL/ symptom improvement	>Threefold elevation in hepatic enzyme with SRL-PEG (%)
				SRL	Pegvisomant	At any time	At study end					
Madsen (2011) (18)	Prospective, OL Duration: 24 weeks Objective: Efficacy with reduced SRL dose	Well controlled on SRL monotherapy	SRL monotherapy	LAN 80 mg/ month or OCT 10–30 mg/month	–	NA (comparable IGF-1 at baseline and end of study in both groups)		NA	NA	Similar in both groups	Similar in both groups	17
			SRL-PEG with SRL dose halved	Baseline SRL dose halved	15–30 mg 2×/week			52.5 (range: 30–60)				
Bianchi (2013) (62)	Retrospective, observational, real-life study Duration: 6 years Objective: efficacy and safety	≥ 12 months inadequate control	PEG-SRL (n = 27)	LAN 120 mg/ month or OCT 30 mg/ month	Starting dose: 10 mg/day (adjusted according to IGF-1 by individual managing physicians)	66.7	55.5	140	Decrease: 3.7% vs 0 (ns)	NA	NA	11.1[j]
			PEG monotherapy (n = 35)	–		82.8 (ns)	80 (p <0.05)	105 (ns)				
Muhammad (2018) (61)	Prospective, OL Duration: 24 weeks Objective: efficacy of PAS monotherapy or PAS-PEG in patients previously well controlled on SRL-PEG	Well controlled with SRL-PEG (mean 134 mg/ week)	PAS monotherapy	PAS 60 mg/ month	–	93.3		PEG sparing effect of 66%	NA	Rise in FBG (6.1–9.1 mmol/L) Rise in HbA1c (6.1–7.3%) Incidence of DM: 33–69%	NA	Nil
			PAS-PEG	PAS 60 mg/ month	61 mg/week (50% reduction from baseline)	67.4						

Somatostatin receptor ligand-pegvisomant cost-effectiveness studies											
Bonert (2020) (52)	Prospective, randomized Duration: 24–32 weeks Objective: cost-effectiveness of SRL-PEG combination	≥ 3 months controlled on SRL monotherapy (63%) inadequate control (37%)	High-dose SRL + Weekly PEG	LAN 120 mg/month or OCT 30 mg/month	40–160 mg/week	End of study: 93.3	NA	NA	Similar in all groups	NA	5.8
			Low-dose SRL + Weekly PEG	LAN 60 mg/month or OCT 10 mg/month	40–160 mg/week	95.7					
			Low-dose SRL + Daily PEG	LAN 60 mg/month or OCT 10 mg/month	15–60 mg/day	100					
			PAS-PEG	PAS 60 mg/month	61 mg/week (50% reduction from baseline)	67.4					

PAS pasireotide LAR, *PEG* pegvisomant, *SRL* long-acting somatostatin receptor ligand, *QoL* quality of life, *OL* open-label, *LAN* lanreotide, *OCT* octreotide LAR, *OGTT* 75 g oral glucose tolerance test, *NA* not applicable, *ns* not significant

[a]Different study criteria for IGF-1 normalization: defined by either end-of-study IGF-1, or lowest IGF-1 achieved

[b]Previous pituitary surgery: 1/4; primary medical therapy: 3/4; none had radiotherapy

[c]Previous pituitary surgery: 2/14; primary medical therapy: 11/14; one patient had radiotherapy

[d]Inclusion criteria: responders to daily PEG monotherapy (presumed previously uncontrolled on SRL therapy) or partial responders to the highest marketed doses of either PEG at 3 months or SRL at 6 months

[e]Post hoc analysis: eight patients whose mean IGF-1 levels were similar while on pegvisomant monotherapy and during the co-administration period were able to reduce their weekly pegvisomant dose by 50%

[f]Defined as >2 × ULN in this study

[g]None had radiotherapy

[h]2/3 patients with elevations >10 × ULN received OCT 60 mg/28 days; vs 3.7 and 3.5 for PEG and OCT monotherapy, respectively

[i]12/21 patients who did not achieve normal IGF-1 received PEG <20 mg/day

[j]Vs. 14.3 in PEG monotherapy group (ns)

62% of patients on PEG-OCT LAR had a normal IGF-1 at 40 weeks. Interestingly, in this study, there was no difference in efficacy between this group and those randomized to PEG monotherapy. In a recent analysis of the ACROSTUDY (a long-term international observational study of patients taking PEG combined with SRLs), IGF-1 was normal in 62% of patients at 4 years [50]. Of note, however, is that in this real-world clinical study, patients could switch treatment categories, and at 7 years after the start of PEG, only 44% of patients remained in the original PEG-SRL treatment category.

Differences in treatment and efficacy definitions may account for differences in the reported study outcomes. In particular, studies differed with respect to criteria for normal IGF-1 (below 1.2 × ULN vs below 1.0 × ULN) and with regard to efficacy endpoints. Some studies used lowest IGF-1 achieved at any time point during treatment [46, 47], while others used fixed time point or end of study IGF-1 to define efficacy [48–50]. Furthermore, varying study protocols, patient inclusion criteria, dosing regimens, and lack of SRL dose escalation [51] and IGF-1 assays may also have contributed to the observed differences.

Secondary Efficacy Endpoints

One advantage of SRL-PEG combination therapy over switching from SRL to PEG monotherapy is the potential to reduce the PEG dose needed to normalize IGF-1 levels. In the aforementioned randomized controlled trial by Trainer et al., PEG doses were 5 mg/day less (15 mg/day vs 20 mg/day) when used as part of combination therapy, as compared to monotherapy [49]. Van der Lely et al. [48] also showed in post hoc analyses that weekly PEG doses could also be reduced by about half in patients whose IGF-1 levels were similar during PEG monotherapy and combination therapy. In a similar fashion, SRL dosing may also be reduced when PEG is introduced. In one study, the addition of PEG (median dose 52.5 mg/week) allowed a 50% reduction in SRL dose in patients previously well controlled on SRL monotherapy [52]. There is, however, significant inter-individual variation in the PEG dose required to normalize IGF-1 in patients with acromegaly with limited clinical data to specifically guide dosing and titration when PEG is added to a SRL treatment regime. Recently, based on a multivariable prediction model, IGF-1 x ULN (but not GH) and body weight beyond a threshold of 100 kg were found to be positively associated with the normalization dose in patients on combination therapy [53].

The cost effectiveness of SRL-PEG combination therapy has been evaluated in a prospective, randomized, open-label, parallel arm study [54]. Sixty patients stratified by SRL dose required for IGF-1 normalization were randomized to three arms: (Arm A) high-dose SRL (LAN 120 mg or OCT LAR 30 mg, monthly) plus weekly PEG 40–160 mg/week, (Arm B) low-dose SRL (LAN 60 mg or OCT LAR 10 mg, monthly) plus weekly PEG 40–160 mg/week, and (Arm C) low-dose SRL (LAN 60 mg or OCT LAR 10 mg, monthly) plus daily PEG (15–60 mg/day). Low-dose SRL plus weekly PEG was the most cost-effective, achieving IGF-1

normalization in 95.7%, a rate that was independent of previous SRL-responsiveness and similar to the two other treatment arms (93.3% and 100% in Arms A and C, respectively).

Another advantage of a SRL-PEG combination treatment is tumor shrinkage or tumor control [47]. Significant tumor volume reduction (TVR) of >20% has been reported in 13–19% of patients [47, 55–57]. This is in contrast to PEG monotherapy whereby tumor growth has been reported, albeit in the minority of patients [21].

In addition, first-generation SRLs have been found to be effective in reducing headache, and in patients who remain biochemically uncontrolled, the addition of PEG may achieve the goal of IGF-1 normalization, while maintaining the benefits of symptom relief with SRLs [58]. Furthermore, one study showed that the addition of PEG at a weekly dose of 40 mg resulted in improvement in quality of life (QoL) scores in patients already biochemically controlled on first-generation SRLs [59]. In this double-blind, placebo-controlled cross-over study, the addition of PEG improved acromegaly-specific QoL despite an absence of significant IGF-1 changes.

The effects of medical therapies on acromegaly complications are less well established. Most studies demonstrate a modest negative impact of first-generation SRLs on glucose homeostasis [60, 61]. Meta-analyses of prospective interventional studies showed that though the effect on fasting plasma glucose (FPG) was neutral, SRL treatment reduced insulin levels and increased after-load glucose, leading to increased hemoglobin A1c, an effect that was proportionate to IGF-1 and GH lowering [62]. Conversely, PEG improves FPG, glucose tolerance, and hemoglobin A1c in patients when used as monotherapy and in those switched from SRLs to PEG [63–65]. Of note, in a meta-analysis of 13 prospective interventional studies of PEG monotherapy treatment, Feola et al. demonstrated that these positive effects on glucose metabolism were independent of disease control [66].

Compared to SRL monotherapy, several small studies have demonstrated improvements in glucose tolerance with the addition of PEG, but no significant differences in FPG, hemoglobin A1c, insulin resistance, or beta-cell function [52, 67, 68]. In one prospective study of 50 patients, FPG levels were lower during SRL-PEG combination therapy than PEG monotherapy among patients biochemically controlled, declining further with withdrawal of SRL therapy and maintenance of PEG monotherapy. A similar effect on glucose tolerance was observed in patients with active disease [69]. However, in the aforementioned meta-analysis by Feola et al. [66], based on five SRL-PEG studies, besides a decrease in fasting plasma insulin, there was no significant effect on other parameters, signifying that overall, adding PEG may mitigate the negative effect of SRLs on glucose metabolism toward a neutral balance. Somatostatin receptor ligand-PEG combination may therefore be especially beneficial in patients with diabetes who have persistently elevated IGF-1 with either drug when used as monotherapy.

Auriemma et al. [70] reported significant improvement in left ventricular mass index (LVMi) and diastolic function with the addition of PEG to SRL treatment, both at 12 months, and in the long term (5 years). Cardiac structure and performance correlated with PEG dose, but not IGF-1 levels, suggesting a potentially

intrinsic role of PEG in blocking cardiac GH receptors, over and above the effects of IGF-1 normalization and improvement in metabolic parameters, with regard to acromegalic cardiomyopathy. The significance of this finding needs further investigation.

Adverse Effects

Transient two- to threefold elevation in liver enzymes has been reported in 11–15% of patients on SRL-PEG combination treatment [47, 48], significantly >1.5–5.2% risk reported with PEG monotherapy in clinical practice studies [18, 19]. Incidence is highest particularly in the first year following treatment and especially in patients on high-dose SRLs [49]. No correlation has, however, been observed between PEG dose and the degree of transaminitis [46, 47]. It is hypothesized that the increase in intrahepatic fat content with combination therapy may account for elevated liver enzymes [52]. Patients with elevations >3 × ULN need close monitoring, and cholelithiasis should be ruled out. Discontinuation of therapy and a liver biopsy is recommended if liver enzymes are more than tenfold elevated [47].

Pasireotide Long-Acting Release and Pegvisomant (PAS-PEG)

Twenty percent of patients resistant to maximum doses of first-generation SRLs may benefit from a switch to PAS monotherapy, achieving biochemical control and an improvement in acromegaly symptom scores [15, 16]. Consistent GH and IGF-1 lowering is seen for up to 6 years [71], and tumor volume reduction is equal or slightly superior compared to the first-generation SRLs [16, 72].

Primary Efficacy Endpoints

A combination of PAS-PEG may, therefore, confer an additional advantage over SRL-PEG. Recently, a PEG-sparing effect has been demonstrated in patients on PAS-PEG combination therapy, as compared to first-generation SRL-PEG combination. In a prospective open-label Pegvisomant and First-Generation Somatostatin Analogues (PAPE Study), patients who were well controlled with SRL-PEG (IGF-1 <1.2 × ULN) were switched to either PAS as monotherapy or a combination with PEG [73]. Mean PEG dose was 134 mg/week at baseline. After a 50% reduction in PEG weekly dose to 60 mg/week, 46/61 (75.4%) patients had elevated IGF-1 (1.59 × ULN), following, which first-generation SRLs were switched to monthly PAS 60 mg. Normalization of IGF-1 was achieved in 31/46 patients (67.4%) at 24 weeks despite the reduced PEG dose. This increased to 71.7% at 48 weeks in an extension study, albeit with 40% achieving <50% PEG dose reduction at that time point [74].

Overall, at 24 weeks, a cumulative 66% PEG-sparing effect was observed with the switch from first-generation SRLs to PAS, which reduced to 52% at 48 weeks.

Secondary Efficacy Endpoints

There is limited data on tumor response with PAS-PEG combination therapy. However, PAS monotherapy studies show that TVR occurs more frequently in patients using PAS than in patients whose disease is inadequately controlled on first-generation SRLs (54% vs 42%), with a 25% TVR observed in the former and 18% reduction observed in the latter [16]. Theoretically, there may, therefore, be a beneficial effect on tumor response compared to patients on SRL-PEG combination [75].

In the PAPE study, authors observed a significant improvement in global AcroQoL with greatest improvements observed in the physical dimension; improvement in QoL was associated mainly with improvement in symptoms of fatigue and headache [75].

A published small case series also highlights the role of PAS-PEG in treatment-resistant acromegaly. Six patients with giant, invasive pituitary adenomas and persistent disease resistant to first-generation SRLs received second-line medical therapy, including SRL-PEG and PAS monotherapy. After failure of all other treatments, biochemical control was finally achieved only through combination therapy with PAS and PEG [76]. Of note, in this case series, a greater SSTR5 and lower SSTR2 expression in the pituitary adenoma was found in those responsive to this combination, as compared to a control of patients resistant to SRLs but controlled with other treatments such as PAS monotherapy, PEG monotherapy, or SRL-PEG. Though in vitro studies suggest a lower SST2/SSTR5 expression in PAS-responders [77], an in vivo study demonstrated that the IGF-1 lowering effects of PAS treatment seemed to be mainly driven by SSTR2 expression as opposed to SSTR5 [78]. Further studies are needed to ascertain which patients will benefit the most from PAS-PEG combination.

Triple combination therapy is rare; however, a combination of PAS, PEG, and cabergoline has been reported to be effective in IGF-1 normalization in a patient resistant to all other treatments [79].

Adverse Effects

While the PAS safety profile is otherwise comparable to first-generation SRLs, PAS is associated with a greater frequency and degree of hyperglycemia-related adverse events [16, 72, 80] that can be explained by its affinity binding. Glucagon-producing pancreatic α-cells predominantly express SSTR2, whereas insulin-producing β-cells mainly express SSTR2 and SSTR5. By binding with high affinity to SSTR5, PAS suppresses insulin secretion, but only modestly inhibits glucagon secretion [81], leading to hyperglycemia. As in PAS monotherapy, hyperglycemia is also

commonly encountered with PAS-PEG treatment. In the PAPE study, FPG increased significantly after the start of PAS treatment, rising from 6.1 mmol/L (95% CI 5.9–6.3) to 9.1 mmol/L (95% CI 8.1–10.1), and hemoglobin A1c rising from 6.1% (95% CI 5.9–6.3) to 7.3% (95% CI 6.9–7.7). The incidence of diabetes mellitus doubled from 33% at baseline to 69% after 24 weeks, with baseline hemoglobin A1c being the most important predictor for development of diabetes. Incidence of diabetes increased further to 77% at 48 weeks of treatment. Most patients required treatment with a combination of metformin and a dipeptidyl peptidase 4 (DPP-4) inhibitor. Nine of 59 patients discontinued PAS-LAR due to severe hyperglycemia, which improved after switching back to first-generation SRL-PEG treatment [73, 74]. Of note, no significant elevation in liver enzymes was observed in patients in the PAPE study.

Therefore, the PEG-sparing effect of PAS may be most beneficial to patients without diabetes using low PEG doses (≤80 mg/week) during combination therapy with first-generation SRLs. Close monitoring for hyperglycemia is recommended in all patients treated with PAS. Patients whose disease is biochemically controlled with first-generation SRL-PEG but who develop symptoms toward the fourth week after SRL administration may also have symptomatic relief after switching to PAS-PEG combination [75].

Cabergoline and Pegvisomant Combination Treatment

Limited data is available on cabergoline-PEG (CAB-PEG) combination therapy. In the only prospective trial to date, this combination therapy was found to be more effective than either drug used alone [82]. Twenty-four patients with active disease (mean IGF-1 1.8 × ULN) on no treatment or after withdrawal of DAs or SRLs were treated with cabergoline monotherapy titrated to a maximum dose of 3.5 mg/week. Only two achieved normal IGF-1 levels after 18 weeks. The addition of PEG 10 mg/day for 12 weeks normalized IGF-1 in 13 (68%). When cabergoline was withdrawn, only five patients (26%) continued to have normal IGF-1 levels and demonstrated greater efficacy with the combination than either treatment as monotherapy.

In another retrospective observational study, 14 patients partially resistant to first-generation SRLs and with elevated IGF-1 (median 1.6 × ULN) were placed on PEG monotherapy (mean 20 mg/day) [83]. The addition of cabergoline (final dose 1.5 mg/week) normalized IGF-1 in 4 patients (28%) after 18 months. It should be noted that all four had received prior radiotherapy. The relatively lower dose of cabergoline used, as compared to that commonly required in acromegaly, may account for the lower efficacy observed in this study. The nadir IGF-1 achieved, but not the rate of IGF-1 normalization was significantly associated with baseline prolactin levels. No significant TVR was observed in this study. Based on the ACROSTUDY [50], at 4 years, IGF-1 normalization in patients on CAB-PEG was similar to patients on SRL-PEG combination treatments (63% and 62%, respectively), though as previously noted, patients could switch between treatment categories.

Overall, as compared to PEG monotherapy, an increased use of combination therapy with SRLs or DA has increased, from 20% in 2003 to 54% in 2012. No significant impact on hepatic function has been reported with this CAB-PEG combination treatment and, overall, appears to be well-tolerated [82, 83]. While no data is available, based on PEG monotherapy studies, a CAB-PEG combination treatment is likely to have a neutral, if not positive, effect on glycemic control.

Conclusion

The management of patients with acromegaly who are inadequately controlled after surgery and first-line medical therapy with first-generation SRLs remains challenging. While further SRL dose optimization, tumor debulking, or switching to PAS or PEG monotherapy may be options, combination therapy should also be considered. In particular, first-generation SRL-PEG combination treatment leads to good biochemical control in the majority and is recommended in patients with no significant response to first-generation SRLs. In those who respond well, reduction in individual drug dosage and frequency of subcutaneous PEG injections may be possible thereafter, which may be both cost-effective and improve QoL. Availability of OOC might increase combination therapy use as patients will only require one injectable therapy. Furthermore, in patients with mild deterioration in glycemic control with first-generation SRLs, the addition of PEG may negate this effect. As compared to PEG monotherapy, this combination may also provide additional symptom relief and TVR and may be considered in patients with large remnant tumor volumes.

In patients with uncontrolled disease, tumor growth, or persistent symptoms despite high doses of first-generation SRL-PEG, switching to PAS-PEG is a viable option. A PEG-sparing effect may also be observed in patients taking SRL-PEG on low PEG doses of 80 mg/week or less, if switched to PAS-PEG. This again allows for a reduction in PEG dose and injection frequency. These benefits, however, have to be balanced against the propensity of the PAS-PEG combination to worsen glycemic control and may not be suitable in patients with underlying diabetes mellitus.

The addition of the relatively inexpensive, well-tolerated, and orally administered cabergoline to SRL treatment is most likely to be effective in patients with mild IGF-1 elevations 1.5–2 × ULN, though patients will need to be monitored for treatment escape. While less data is available, the combination of PEG and cabergoline may be useful in a subset of patients with mild IGF-1 elevations, particularly in the setting of SRL-intolerance, if the cost of SRL-PEG is prohibitive, or in patients with poorly controlled diabetes.

Ultimately, individualization remains key to the management of patients with acromegaly and patient characteristics, including disease activity, tumor volume and location, symptoms and comorbidities, patient preferences, and QoL, and the cost effectiveness of combination therapy needs to be considered [84].

Conflict of Interest MF has received research support to OHSU as a principal investigator from Chiasma, Crinetics, Ionis, Novartis and has received occasional scientific consulting from Chiasma, Crinetics, Ionis, Ipsen, Novartis, Pfizer, Recordati.

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References

1. Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51.
2. Gadelha MR, Kasuki L, Lim DST, Fleseriu M. Systemic complications of acromegaly and the impact of the current treatment landscape: an update. Endocr Rev. 2019;40(1):268–332.
3. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest. 2009;119(11):3189–202.
4. Melmed S. Pituitary-tumor endocrinopathies. N Engl J Med. 2020;382(10):937–50.
5. Jane JA Jr, Starke RM, Elzoghby MA, Reames DL, Payne SC, Thorner MO, et al. Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. J Clin Endocrinol Metab. 2011;96(9):2732–40.
6. Starke RM, Raper DM, Payne SC, Vance ML, Oldfield EH, Jane JA Jr. Endoscopic vs microsurgical transsphenoidal surgery for acromegaly: outcomes in a concurrent series of patients using modern criteria for remission. J Clin Endocrinol Metab. 2013;98(8):3190–8.
7. Caron PJ, Bevan JS, Petersenn S, Flanagan D, Tabarin A, Prevost G, et al. Tumor shrinkage with lanreotide Autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. J Clin Endocrinol Metab. 2014;99(4):1282–90.
8. Howlett TA, Willis D, Walker G, Wass JA, Trainer PJ, Group UKARS. Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists. Clin Endocrinol. 2013;79(5):689–99.
9. Mercado M, Borges F, Bouterfa H, Chang TC, Chervin A, Farrall AJ, et al. A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. Clin Endocrinol. 2007;66(6):859–68.
10. Carmichael JD, Bonert VS, Nuno M, Ly D, Melmed S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. J Clin Endocrinol Metab. 2014;99(5):1825–33.
11. Mazziotti G, Giustina A. Effects of lanreotide SR and Autogel on tumor mass in patients with acromegaly: a systematic review. Pituitary. 2010;13(1):60–7.
12. Brzana J, Yedinak CG, Gultekin SH, Delashaw JB, Fleseriu M. Growth hormone granulation pattern and somatostatin receptor subtype 2A correlate with postoperative somatostatin receptor ligand response in acromegaly: a large single center experience. Pituitary. 2013;16(4):490–8.
13. Varlamov EV, Wood MD, Netto JP, Thiessen J, Kim J, Lim DST, et al. Cystic appearance on magnetic resonance imaging in bihormonal growth hormone and prolactin tumors in acromegaly. Pituitary. 2020;23(6):672–80.
14. Colao A, Auriemma RS, Lombardi G, Pivonello R. Resistance to somatostatin analogs in acromegaly. Endocr Rev. 2011;32(2):247–71.
15. Bronstein MD, Fleseriu M, Neggers S, Colao A, Sheppard M, Gu F, et al. Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: crossover extension to a randomized, double-blind, Phase III study. BMC Endocr Disord. 2016;16:16.
16. Gadelha MR, Bronstein MD, Brue T, Coculescu M, Fleseriu M, Guitelman M, et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2(11):875–84.

17. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, et al. A consensus statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552–61.
18. Freda PU, Gordon MB, Kelepouris N, Jonsson P, Koltowska-Haggstrom M, van der Lely AJ. Long-term treatment with pegvisomant as monotherapy in patients with acromegaly: experience from acrostudy. Endocr Pract. 2015;21(3):264–74.
19. Schreiber I, Buchfelder M, Droste M, Forssmann K, Mann K, Saller B, et al. Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy evaluation from the German Pegvisomant Observational Study. Eur J Endocrinol. 2007;156(1):75–82.
20. van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet. 2001;358(9295):1754–9.
21. Leonart LP, Tonin FS, Ferreira VL, Fernandez-Llimos F, Pontarolo R. Effectiveness and safety of pegvisomant: a systematic review and meta-analysis of observational longitudinal studies. Endocrine. 2019;63(1):18–26.
22. Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327–35.
23. Fleseriu M. The role of combination medical therapy in acromegaly: hope for the nonresponsive patient. Curr Opin Endocrinol Diabetes Obes. 2013;20(4):321–9.
24. Lim DS, Fleseriu M. The role of combination medical therapy in the treatment of acromegaly. Pituitary. 2017;20(1):136–48.
25. Ambrosio MR, Gagliardi I, Chiloiro S, Ferreira AG, Bondanelli M, Giampietro A, et al. Acromegaly in the elderly patients. Endocrine. 2020;68(1):16–31.
26. Jaffe CA, Barkan AL. Treatment of acromegaly with dopamine agonists. Endocrinol Metab Clin N Am. 1992;21(3):713–35.
27. Cozzi R, Attanasio R, Lodrini S, Lasio G. Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. Clin Endocrinol. 2004;61(2):209–15.
28. Gatta B, Hau DH, Catargi B, Roger P, Tabarin A. Re-evaluation of the efficacy of the association of cabergoline to somatostatin analogues in acromegalic patients. Clin Endocrinol. 2005;63(4):477–8.
29. Jallad RS, Bronstein MD. Optimizing medical therapy of acromegaly: beneficial effects of cabergoline in patients uncontrolled with long-acting release octreotide. Neuroendocrinology. 2009;90(1):82–92.
30. Marzullo P, Ferone D, Di Somma C, Pivonello R, Filippella M, Lombardi G, et al. Efficacy of combined treatment with lanreotide and cabergoline in selected therapy-resistant acromegalic patients. Pituitary. 1999;1(2):115–20.
31. Selvarajah D, Webster J, Ross R, Newell-Price J. Effectiveness of adding dopamine agonist therapy to long-acting somatostatin analogues in the management of acromegaly. Eur J Endocrinol. 2005;152(4):569–74.
32. Puig-Domingo M, Soto A, Venegas E, Vilchez R, Blanco C, Cordido F, et al. Use of lanreotide in combination with cabergoline or pegvisomant in patients with acromegaly in the clinical practice: the ACROCOMB study. Endocrinol Nutr. 2016;63(8):397–408.
33. Vandeva S, Elenkova A, Natchev E, Kirilov G, Tcharaktchiev D, Yaneva M, et al. Treatment outcome results from the Bulgarian Acromegaly Database: adjuvant dopamine agonist therapy is efficient in less than one fifth of non-irradiated patients. Exp Clin Endocrinol Diabetes. 2015;123(1):66–71.
34. Suda K, Inoshita N, Iguchi G, Fukuoka H, Takahashi M, Nishizawa H, et al. Efficacy of combined octreotide and cabergoline treatment in patients with acromegaly: a retrospective clinical study and review of the literature. Endocr J. 2013;60(4):507–15.
35. Mattar P, Alves Martins MR, Abucham J. Short- and long-term efficacy of combined cabergoline and octreotide treatment in controlling igf-I levels in acromegaly. Neuroendocrinology. 2010;92(2):120–7.

36. Vilar L, Azevedo MF, Naves LA, Casulari LA, Albuquerque JL, Montenegro RM, et al. Role of the addition of cabergoline to the management of acromegalic patients resistant to longterm treatment with octreotide LAR. Pituitary. 2011;14(2):148–56.
37. Freda PU, Reyes CM, Nuruzzaman AT, Sundeen RE, Khandji AG, Post KD. Cabergoline therapy of growth hormone & growth hormone/prolactin secreting pituitary tumors. Pituitary. 2004;7(1):21–30.
38. Kasuki L, Dalmolin MD, Wildemberg LE, Gadelha MR. Treatment escape reduces the effectiveness of cabergoline during long-term treatment of acromegaly in monotherapy or in association with first-generation somatostatin receptor ligands. Clin Endocrinol. 2018;88(6):889–95.
39. Fleseriu M, Katznelson L, Clemmons DR, Trainer P, Biermasz NR, Strasburger CJ, et al. Mpowered: study design of a phase 3 head-to-head trial evaluating oral octreotide capsules versus injectable somatostatin analogs in patients with acromegaly. Endocr Pract. 2016;22(2):193–226.
40. https://pubmed.ncbi.nlm.nih.gov/34953531/.
41. Ferone D, Saveanu A, Culler MD, Arvigo M, Rebora A, Gatto F, et al. Novel chimeric somatostatin analogs: facts and perspectives. Eur J Endocrinol. 2007;156(1):S23–8.
42. Jaquet P, Gunz G, Saveanu A, Barlier A, Dufour H, Taylor J, et al. BIM-23A760, a chimeric molecule directed towards somatostatin and dopamine receptors, vs universal somatostatin receptors ligands in GH-secreting pituitary adenomas partial responders to octreotide. J Endocrinol Investig. 2005;28(11):21–7.
43. Vázquez-Borrego MC, Gálvez-Moreno MA, Fuentes-Fayos AC, Venegas-Moreno E, Herrera-Martínez AD, et al. A new generation somatostatin-dopamine analogue exerts potent antitumoral actions on pituitary neuroendocrine tumor cells. Neuroendocrinology. 2020;110(1-2):70–82.
44. Maione L, Garcia C, Bouchachi A, Kallel N, Maison P, Salenave S, et al. No evidence of a detrimental effect of cabergoline therapy on cardiac valves in patients with acromegaly. J Clin Endocrinol Metab. 2012;97(9):1714–9.
45. Kuhn E, Chanson P. Cabergoline in acromegaly. Pituitary. 2017;20(1):121–8.
46. Feenstra J, de Herder WW, ten Have SM, van den Beld AW, Feelders RA, Janssen JA, et al. Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. Lancet. 2005;365(9471):1644–6.
47. Neggers SJ, Franck SE, de Rooij FW, Dallenga AH, Poublon RM, Feelders RA, et al. Long-term efficacy and safety of pegvisomant in combination with long-acting somatostatin analogs in acromegaly. J Clin Endocrinol Metab. 2014;99(10):3644–52.
48. van der Lely AJ, Bernabeu I, Cap J, Caron P, Colao A, Marek J, et al. Coadministration of lanreotide Autogel and pegvisomant normalizes IGF1 levels and is well tolerated in patients with acromegaly partially controlled by somatostatin analogs alone. Eur J Endocrinol. 2011;164(3):325–33.
49. Trainer PJ, Ezzat S, D'Souza GA, Layton G, Strasburger CJ. A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. Clin Endocrinol. 2009;71(4):549–57.
50. Strasburger CJ, Mattsson A, Wilton P, Aydin F, Hey-Hadavi J, Biller BMK. Increasing frequency of combination medical therapy in the treatment of acromegaly with the GH receptor antagonist pegvisomant. Eur J Endocrinol. 2018;178(4):321–9.
51. Fleseriu M. Clinical efficacy and safety results for dose escalation of somatostatin receptor ligands in patients with acromegaly: a literature review. Pituitary. 2011;14(2):184–93.
52. Madsen M, Poulsen PL, Orskov H, Moller N, Jorgensen JO. Cotreatment with pegvisomant and a somatostatin analog (SA) in SA-responsive acromegalic patients. J Clin Endocrinol Metab. 2011;96(8):2405–13.
53. Franck SE, Korevaar TIM, Petrossians P, Daly AF, Chanson P, Jaffrain-Rea ML, et al. A multivariable prediction model for pegvisomant dosing: monotherapy and in combination with long-acting somatostatin analogues. Eur J Endocrinol. 2017;176(4):421–31.
54. Bonert V, Mirocha J, Carmichael J, Yuen KCJ, Araki T, Melmed S. Cost-effectiveness and efficacy of a novel combination regimen in acromegaly: a prospective, randomized trial. J Clin Endocrinol Metab. 2020;105(9):444.

55. Bianchi A, Valentini F, Iuorio R, Poggi M, Baldelli R, Passeri M, et al. Long-term treatment of somatostatin analog-refractory growth hormone-secreting pituitary tumors with pegvisomant alone or combined with long-acting somatostatin analogs: a retrospective analysis of clinical practice and outcomes. J Exp Clin Cancer Res. 2013;32:40.
56. Neggers SJ, de Herder WW, Janssen JA, Feelders RA, van der Lely AJ. Combined treatment for acromegaly with long-acting somatostatin analogs and pegvisomant: long-term safety for up to 4.5 years (median 2.2 years) of follow-up in 86 patients. Eur J Endocrinol. 2009;160(4):529–33.
57. Neggers SJ, van Aken MO, Janssen JA, Feelders RA, de Herder WW, van der Lely AJ. Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. J Clin Endocrinol Metab. 2007;92(12):4598–601.
58. Kreitschmann-Andermahr I, Siegel S, Weber Carneiro R, Maubach JM, Harbeck B, Brabant G. Headache and pituitary disease: a systematic review. Clin Endocrinol. 2013;79(6):760–9.
59. Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X, et al. Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. J Clin Endocrinol Metab. 2008;93(10):3853–9.
60. Grasso LF, Auriemma RS, Pivonello R, Colao A. Adverse events associated with somatostatin analogs in acromegaly. Expert Opin Drug Saf. 2015;14(8):1213–26.
61. Mazziotti G, Floriani I, Bonadonna S, Torri V, Chanson P, Giustina A. Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. J Clin Endocrinol Metab. 2009;94(5):1500–8.
62. Cozzolino A, Feola T, Simonelli I, Puliani G, Pozza C, Giannetta E, et al. Somatostatin analogs and glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. J Clin Endocrinol Metab. 2018. https://doi.org/10.1210/jc.2017-02566
63. Barkan AL, Burman P, Clemmons DR, Drake WM, Gagel RF, Harris PE, et al. Glucose homeostasis and safety in patients with acromegaly converted from long-acting octreotide to pegvisomant. J Clin Endocrinol Metab. 2005;90(10):5684–91.
64. Drake WM, Rowles SV, Roberts ME, Fode FK, Besser GM, Monson JP, et al. Insulin sensitivity and glucose tolerance improve in patients with acromegaly converted from depot octreotide to pegvisomant. Eur J Endocrinol. 2003;149(6):521–7.
65. Higham CE, Rowles S, Russell-Jones D, Umpleby AM, Trainer PJ. Pegvisomant improves insulin sensitivity and reduces overnight free fatty acid concentrations in patients with acromegaly. J Clin Endocrinol Metab. 2009;94(7):2459–63.
66. Feola T, Cozzolino A, Simonelli I, Sbardella E, Pozza C, Giannetta E, et al. Pegvisomant improves glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. J Clin Endocrinol Metab. 2019;104(7):2892–902.
67. De Marinis L, Bianchi A, Fusco A, Cimino V, Mormando M, Tilaro L, et al. Long-term effects of the combination of pegvisomant with somatostatin analogs (SSA) on glucose homeostasis in non-diabetic patients with active acromegaly partially resistant to SSA. Pituitary. 2007;10(3):227–32.
68. Jorgensen JO, Feldt-Rasmussen U, Frystyk J, Chen JW, Kristensen LO, Hagen C, et al. Cotreatment of acromegaly with a somatostatin analog and a growth hormone receptor antagonist. J Clin Endocrinol Metab. 2005;90(10):5627–31.
69. Urbani C, Sardella C, Calevro A, Rossi G, Scattina I, Lombardi M, et al. Effects of medical therapies for acromegaly on glucose metabolism. Eur J Endocrinol. 2013;169(1):99–108.
70. Auriemma RS, Grasso LF, Galdiero M, Galderisi M, Pivonello C, Simeoli C, et al. Effects of long-term combined treatment with somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly. Endocrine. 2017;55(3):872–84.
71. Colao A, Bronstein MD, Brue T, De Marinis L, Fleseriu M, Guitelman M, et al. Pasireotide for acromegaly: long-term outcomes from an extension to the Phase III PAOLA study. Eur J Endocrinol. 2020;182(6):583.
72. Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014;99(3):791–9.

73. Muhammad A, van der Lely AJ, Delhanty PJD, Dallenga AHG, Haitsma IK, Janssen J, et al. Efficacy and safety of switching to pasireotide in patients with acromegaly controlled with pegvisomant and first-generation somatostatin analogues (PAPE Study). J Clin Endocrinol Metab. 2018;103(2):586–95.
74. Muhammad A, Coopmans EC, Delhanty PJD, Dallenga AHG, Haitsma IK, Janssen J, et al. Efficacy and safety of switching to pasireotide in acromegaly patients controlled with pegvisomant and somatostatin analogues: PAPE extension study. Eur J Endocrinol. 2018;179(5):269–77.
75. Coopmans EC, Muhammad A, van der Lely AJ, Janssen J, Neggers S. How to position pasireotide LAR treatment in acromegaly. J Clin Endocrinol Metab. 2019;104(6):1978–88.
76. Chiloiro S, Bima C, Tartaglione T, Giampietro A, Gessi M, Lauretti L, et al. Pasireotide and pegvisomant combination treatment in acromegaly resistant to second-line therapies: a longitudinal study. J Clin Endocrinol Metab. 2019;104(11):5478–82.
77. Gatto F, Feelders RA, Franck SE, van Koetsveld PM, Dogan F, Kros JM, et al. In vitro head-to-head comparison between octreotide and pasireotide in GH-secreting pituitary adenomas. J Clin Endocrinol Metab. 2017;102(6):2009–18.
78. Muhammad A, Coopmans EC, Gatto F, Franck SE, Janssen J, van der Lely AJ, et al. Pasireotide responsiveness in acromegaly is mainly driven by somatostatin receptor subtype 2 expression. J Clin Endocrinol Metab. 2019;104(3):915–24.
79. Ciresi A, Radellini S, Guarnotta V, Giordano C. Efficacy of combined treatment with pasireotide, pegvisomant and cabergoline in an acromegalic patient resistant to other treatments: a case report. BMC Endocr Disord. 2018;18(1):2.
80. Fleseriu M, Rusch E, Geer EB, Investigators AS. Safety and tolerability of pasireotide long-acting release in acromegaly-results from the acromegaly, open-label, multicenter, safety monitoring program for treating patients who have a need to receive medical therapy (ACCESS) study. Endocrine. 2017;55(1):247–55.
81. Henry RR, Ciaraldi TP, Armstrong D, Burke P, Ligueros-Saylan M, Mudaliar S. Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. J Clin Endocrinol Metab. 2013;98(8):3446–53.
82. Higham CE, Atkinson AB, Aylwin S, Bidlingmaier M, Drake WM, Lewis A, et al. Effective combination treatment with cabergoline and low-dose pegvisomant in active acromegaly: a prospective clinical trial. J Clin Endocrinol Metab. 2012;97(4):1187–93.
83. Bernabeu I, Alvarez-Escola C, Paniagua AE, Lucas T, Pavon I, Cabezas-Agricola JM, et al. Pegvisomant and cabergoline combination therapy in acromegaly. Pituitary. 2013;16(1):101–8.
84. https://pubmed.ncbi.nlm.nih.gov/33079318/.