

Original article

Patterns of pharmacologic treatment
in US patients with acromegaly

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Abstract**Objective:**

To establish a baseline pattern of care across academic and community settings, it is important to examine the contemporary treatment of acromegaly. We characterized medical treatment patterns for acromegaly in the US to develop a basis for tracking concordance with guidelines.

Research design and methods:

Acromegaly patients were identified in two commercial claims databases for this retrospective analysis. Study subjects had ≥ 2 medical claims with acromegaly (ICD-9-CM code 253.0) and ≥ 1 claim for pharmacotherapy (bromocriptine, cabergoline, octreotide SA, octreotide LAR, lanreotide, or pegvisomant) in the study timeframe (1 January 2002–31 December 2013). Patients were considered newly treated if they were continuously enrolled for ≥ 6 months before first observed treatment and had no claim for pharmacologic treatment during that time. Outcomes included various pharmacotherapies, including combination treatments, and differences between lines of therapy.

Results:

A total of 3150 patients had ≥ 1 pharmacotherapy (mean age: 46.5 years; 50.1% were female); 1471 were newly treated. Somatostatin receptor ligands (SRLs) were the most common drug class used first line (57.2%); cabergoline (27.8%) was the most common treatment, followed by octreotide LAR (22.3%) and lanreotide (19.7%). SRLs were also the most commonly used second-line (42.8%) and third-line pharmacotherapies (43.9%), with combination therapy (23.2%) and octreotide LAR (19.8%) as the most commonly used treatments, respectively.

Conclusions:

This study, representing the largest claims-based analysis of acromegaly to date, used two databases across a 12 year period to examine complex treatment patterns in a difficult-to-study disease. Although wide variation in acromegaly treatment patterns exists in US clinical practice, in first-line, second-line, and third-line therapy, SRL was the most commonly used drug class. Drug combinations also varied considerably across lines of therapy. The switching between different monotherapies and varied use of drugs in combination may suggest an unmet need for alternative treatment options. Our claims-based technique of examining treatment patterns may be used for other rare diseases, although high censoring rates may be a challenge.

Introduction

Acromegaly is a rare, slowly progressive, acquired disorder resulting from excessive growth hormone (GH) production, usually from a hormonally active pituitary adenoma^{1–3}. Anatomic changes and metabolic dysfunction as a result of elevated GH and insulin-like growth factor 1 (IGF-1) occur as a result⁴. The goal of treatment is to reduce GH and IGF-1 levels to normal,

which in turn alleviates comorbidities associated with acromegaly and reduces the mortality rates of patients with acromegaly to those expected in the general population^{4,5}. Surgery is considered first-line therapy for most cases of acromegaly⁴⁻⁶. A variety of pharmacologic treatments are available for patients in whom surgery is contraindicated or who require treatment following surgery.

One important class of medications for acromegaly is the somatostatin receptor ligands (SRLs). Somatostatin is the primary negative regulator of pituitary GH release⁷. Somatotrophic cells predominantly express two somatostatin receptor subtypes, SSTR-2 and SSTR-5, both of which signal the pituitary gland to suppress GH secretion. More than 90% of GH-secreting tumors express these two receptors, and receptor-mediated suppression of GH remains intact in pituitary tumors¹. Recognition of this physiologic phenomenon led to the development of SRLs in the mid-1980s; these agents are effective in normalizing serum GH in 56% of patients with acromegaly, normalizing IGF-1 in 55%, and inducing a significant degree of tumor shrinkage in up to 75%⁸⁻¹⁰.

SRLs such as short-acting (SA) or long-acting (LAR) octreotide or lanreotide are generally recommended as first-line medical therapy (e.g., in patients who cannot tolerate, or have inadequate results from, surgery)⁴⁻⁶. Existing guidelines are less in agreement regarding second-line and subsequent therapy. For example, the 2011 guidelines by the American Association of Clinical Endocrinologists (AACE) recommend adding a dopamine agonist (DA) such as cabergoline to SRL therapy for non-responders⁶. In contrast, the 2014 guidelines from the Acromegaly Consensus Group suggest different treatment paths for patients failing initial medical therapy depending on whether the patient is partially controlled (either increase SRL or combine SRL and pegvisomant therapy) or uncontrolled (switch to pegvisomant)⁴.

In light of the new Acromegaly Consensus Group guidelines, it may be instructive to examine the contemporary medical treatment of acromegaly, in order to establish a baseline pattern of care across academic and community settings. Doing so will facilitate future comparison of treatment patterns before and after institution of these guidelines and the relative effectiveness of various therapeutic interventions or sequences of care, all of which may inform future guideline development.

The objective of this study was to characterize medical treatment patterns for acromegaly in the United States in order to develop a basis for tracking concordance with existing and future guidelines. Our claims-based retrospective analysis included examination of first-, second-, and third-line pharmacologic treatments.

Patients and methods

This was a retrospective cohort study using two commercial claims databases, Truven MarketScan and IMS Health PharMetrics, from 1 January 2002 to 31 December 2013. The databases were combined to maximize sample size. Both databases are Health Insurance Portability and Accountability Act (HIPAA)-compliant administrative claims databases containing de-identified adjudicated pharmacy and medical claims submitted for payment by providers, healthcare facilities, and pharmacies. We identified all pharmacologically treated acromegaly patients using the following inclusion criteria: 1) at least two medical claims with acromegaly (ICD-9-CM [International Classification of Diseases, 9th Revision, Clinical Modification] code 253.0) in any diagnosis field in the study timeframe, and 2) at least one claim of pharmacologic treatment associated with acromegaly (*Supplementary Online Appendix*) in the study timeframe.

Patients were classified as newly treated if they were continuously enrolled for at least 6 months prior to the first observed treatment and had no claim of pharmacologic treatment during that time. Treatments were identified both from pharmacy and medical claims using National Drug Codes (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes, respectively. The course of pharmacologic treatment was defined as the period extending from the first (index) treatment claim until 1) the date of the last claim for that treatment (plus the days of supply), 2) the date the patient switched to another pharmacologic treatment, or 3) disenrollment, whichever came first. Combination treatment was defined as treatment with ≥ 2 medications with an overlap of ≥ 90 days.

For all patients, we identified age (during the year of first observed pharmacologic treatment), sex, and medications to treat acromegaly (bromocriptine, cabergoline, octreotide SA, octreotide LAR, lanreotide, and pegvisomant). Pharmacologic treatment distributions were calculated based on data from 2008 onward, due to the introduction of lanreotide for the treatment of acromegaly in 2007. All descriptive statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Three thousand one hundred fifty patients in the study cohort received at least one pharmacologic treatment for acromegaly (Table 1). Mean age of the patients was 46.5 years, and 50.1% were female. One thousand four hundred seventy-one patients were observed to newly start treatment with a pharmacologic agent (e.g., had a 6 month treatment-free period before first use). Examining changes in treatment over time, overall, the most common first line

of treatments were somatostatin analogues (SSA) (octreotide LAR, octreotide SA, and lanreotide), followed by dopamine agonists (cabergoline and bromocriptine), followed by growth hormone receptor agonist pegvisomant (Figure 1). Lanreotide received US Food and Drug Administration (FDA) approval for acromegaly in 2007, and it represented 27.4% of pharmacologic treatment by 2013. Bromocriptine was used in 15.8% of cases in 2002 and 7.5% in 2013.

The SRLs were the most common class of pharmacologic therapies used as first-line agents (57.2%; Figure 2). Cabergoline (27.8%) was the most common treatment, followed by octreotide LAR (22.3%) and lanreotide (19.7%). Drug combinations were used least commonly as first-line pharmacologic therapy (0.1%).

Among patients who received second-line pharmacologic therapy, SRLs (42.8%) were the most common

medications used; octreotide LAR (19.1%) was the single most common drug (Figure 2). Drug combinations were used in 23.2% of patients; SRLs were used in 89.5% of patients receiving drug combinations, and SRL-pegvisomant only combinations were used in 33.7% (Table 2). The most common combination was octreotide LAR and cabergoline (23.9%). Among patients on a first-line long-acting SRL (octreotide LAR or lanreotide), 23.0% switched to a different long-acting SRL (results not shown). Further, among patients on a first-line long-acting SRL, a higher proportion of patients switched to combination therapy (29.9%) compared to pegvisomant (18.9%) (results not shown).

Among patients who received third-line pharmacologic therapy, SRLs (43.9%) were again the most common class of medication and octreotide LAR (19.8%) the most common drug. Drug combinations were used in 18.6% of patients; SRLs were used in 89.3% of these cases (Table 3).

Table 1. Patient characteristics (n = 3150).

Patient Characteristic	Value
Age in years, mean (SD)	46.5 (12.7)
Age group, no. (%)	
≤40	978 (31.0)
41–50	852 (27.0)
≥51	1320 (41.9)
Female sex, no. (%)	1578 (50.1)
Region, no. (%)	
Midwest	873 (27.7)
Northeast	742 (23.6)
South	1036 (32.9)
West	499 (15.8)

SD = standard deviation.

Discussion

Our study of recent treatment practices in insured patients with acromegaly revealed that cabergoline and octreotide LAR are the most common first-line pharmacologic agents accounting for nearly 22% and 28% of drug treatments, respectively. Octreotide SA is also relatively common, comprising 15.2% of first line pharmacologic treatments. Bromocriptine use decreased over time, but was still used in 7.5% of first-line therapy in 2013. Among patients progressing to second-line treatment, SRLs remain the most common class, with octreotide LAR the most common

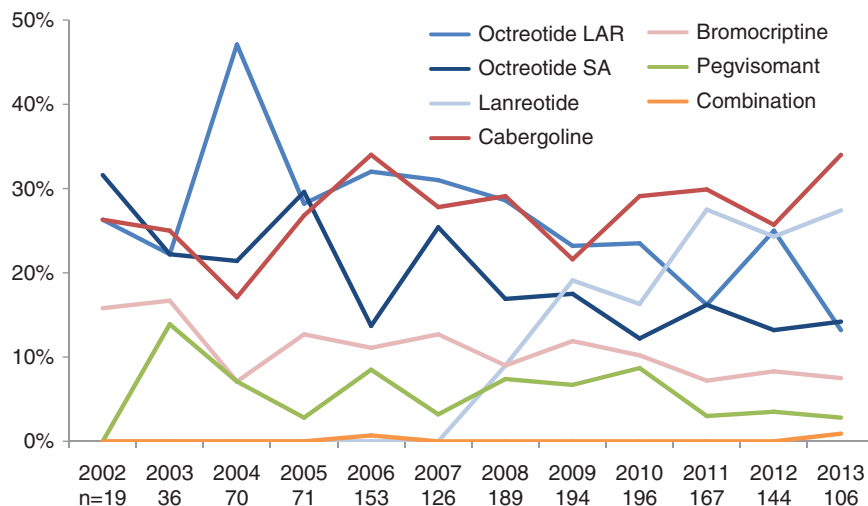


Figure 1. Changes over time in first-line pharmacologic treatment received by newly treated acromegaly patients. Lanreotide was not approved by the US Food and Drug Administration for acromegaly until August 2007. Combinations were octreotide LAR + cabergoline in 2006 and lanreotide + pegvisomant in 2013.

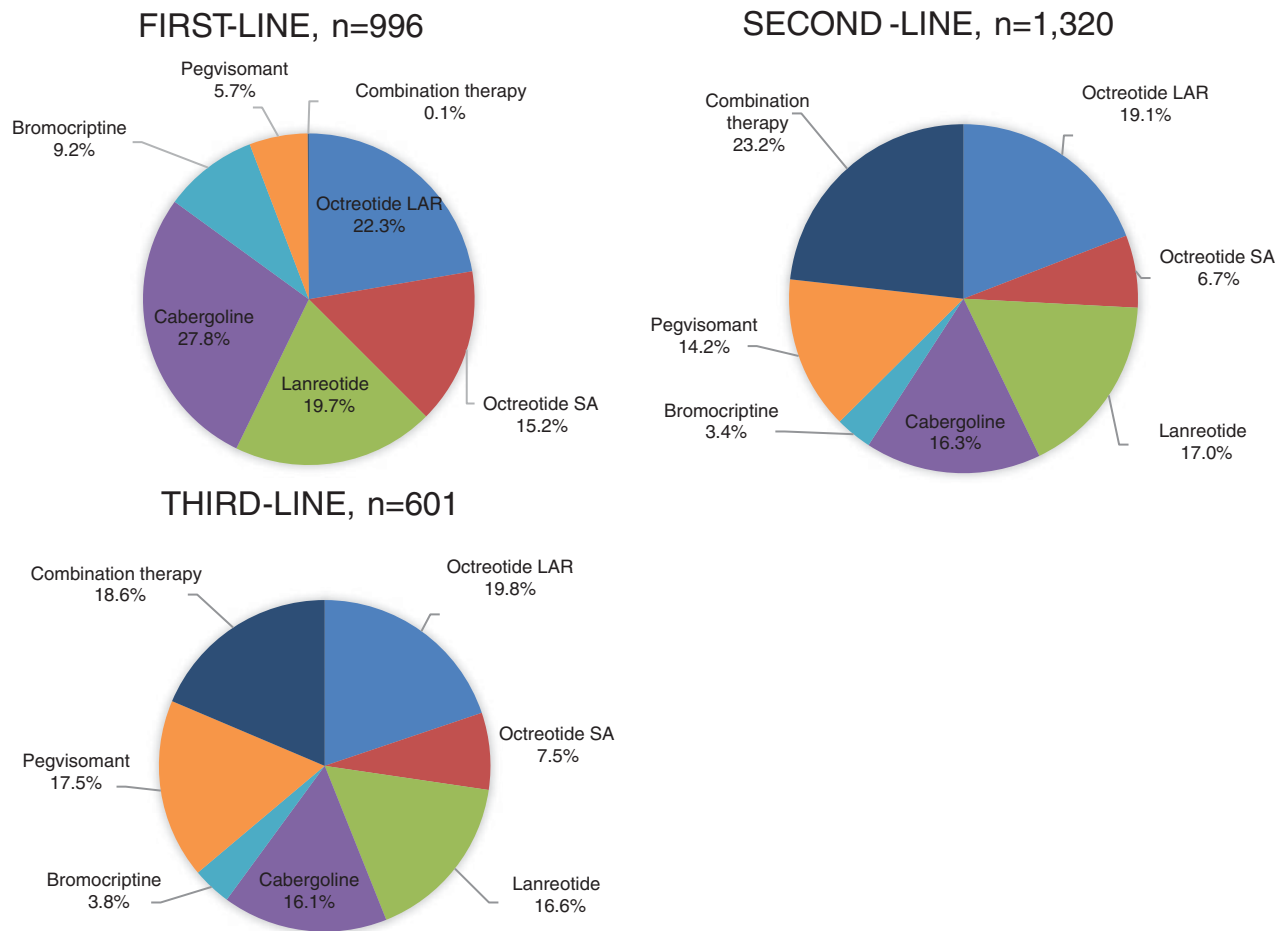


Figure 2. Distribution of pharmacologic treatments given first, second, and third line in acromegaly patients (initiated/switched in 2008 or later).

Table 2. Combinations of drug therapies used as second-line pharmacotherapy (initiated in 2008 or later).

Combination Pharmacologic Treatment (N=306)	N	%
Octreotide LAR + Cabergoline	73	23.86
Lanreotide + Cabergoline	63	20.59
Octreotide LAR + Pegvisomant	55	17.97
Lanreotide + Pegvisomant	37	12.09
Cabergoline + Pegvisomant	29	9.48
Octreotide LAR + Bromocriptine	14	4.58
Octreotide SA + Pegvisomant	11	3.59
Octreotide SA + Cabergoline	5	1.63
Lanreotide + Cabergoline + Pegvisomant	5	1.63
Octreotide SA + Bromocriptine	4	1.31
Lanreotide + Bromocriptine	3	0.98
Bromocriptine + Pegvisomant	3	0.98
Octreotide LAR + Cabergoline + Pegvisomant	3	0.98
Octreotide SA + Cabergoline + Pegvisomant	1	0.33

single agent. Combination therapy used in the second line includes an SRL in nearly 90% of cases. The study examined patients treated from 2002 to 2013, and the major change we found during that period was an increase in

lanreotide and a concomitant fall in bromocriptine after 2007.

Current guidelines recommend SRLs as first-line medical therapy. Octreotide LAR has been commercially available since 1988, compared to 2007 for lanreotide, which may explain its use as the predominate SRL. Lanreotide use increased throughout the study period and cabergoline was typically the most common first-line agent. Clinical practice guidelines suggest using cabergoline in patients with modest disease^{4,6}, but claims databases do not contain information on disease severity, so we could not test whether this was how the drug was being used. The increase in lanreotide use corresponded with a decrease in bromocriptine. Lanreotide, like the dopamine agonists, may be self-administered, making it an attractive option for patients who prefer not to come to the office for treatment¹¹.

Short-acting octreotide use was common. A *post hoc* analysis found 40% of users filled ≤ 30 days, suggesting that, consistent with dose FDA labeling, many patients are given a test dose of SA before beginning octreotide LAR. This practice is not employed by many experienced

Table 3. Combinations of drug therapies used as third-line pharmacotherapy (initiated in 2008 or later).

Combination Pharmacologic Treatment (N=112)	N	%
Lanreotide + Cabergoline	26	23.21
Octreotide LAR + Cabergoline	21	18.75
Octreotide LAR + Pegvisomant	21	18.75
Lanreotide + Pegvisomant	15	13.39
Cabergoline + Pegvisomant	10	8.93
Lanreotide + Cabergoline + Pegvisomant	5	4.46
Octreotide LAR + Bromocriptine	4	3.57
Octreotide SA + Pegvisomant	3	2.68
Bromocriptine + Pegvisomant	2	1.79
Octreotide LAR + Cabergoline + Pegvisomant	2	1.79
Lanreotide + Bromocriptine	1	0.89
Octreotide SA + Cabergoline	1	0.89
Octreotide SA + Cabergoline + Pegvisomant	1	0.89

prescribers of octreotide LAR¹² and may have become less common over time: octreotide SA use declined over the course of our study from 32% of first-line therapy in 2002 to 14% in 2013. Short-acting SRLs remain less expensive than long-acting ones and thus formulary restrictions or voluntary decisions to use less expensive agents may play a role⁶.

There was higher-than-expected bromocriptine use. Bromocriptine, a non-selective DA, became available for the treatment of acromegaly in 1974 and was the first drug to be widely used for this condition¹³. However, in recent years there has been a growing body of evidence demonstrating the efficacy of other options. An acromegaly consensus statement published in 2005¹⁴ recommended the use of DAs as a class (i.e., cabergoline and bromocriptine), by 2009 clear data demonstrated that only cabergoline was efficacious in acromegaly¹⁵. The persistent use of bromocriptine may reflect a variety of barriers to adherence with practice guidelines; despite their good intentions, guidelines have a notoriously limited effect on overcoming 'clinical inertia'^{16–18}. More effective methods of dissemination of updated guidelines may be necessary to improve guideline uptake among providers who treat acromegaly less frequently.

Finally, we observed a wide variety of drug combinations used in the second and third line. Most of these observations were in patients treated before any formal recommendations for such treatment had been published. The majority of combinations included a SRL and either pegvisomant or cabergoline. Neither combination has been subjected to randomized controlled trials, but both appear safe and effective based on prior studies^{19–26}. In particular, the effectiveness of SRL–pegvisomant combination therapy may be due to the increase in GH levels seen with pegvisomant monotherapy being negated by the use of SRLs. GH receptor numbers are reduced through the mechanism of action of SRLs, and in addition SRLs

directly inhibit IGF-1 production. As a result, a reduction of pegvisomant dose is possible when used in combination with SRLs; an IGF-1 normalization rate approaching 100% and a clinically meaningful decrease in tumor size in about 20% of patients have both been observed^{27,29}. There have been no direct comparisons between combination therapy (i.e., SRL and pegvisomant) and pegvisomant monotherapy to date^{4,16}.

There are several reports from European acromegaly registries that, while using medical records rather than the insurance claims we used, present an interesting comparison to our study. In the German Acromegaly Registry database, based on 2013 data, 59% of patients received some medical therapy²⁹. The distribution of therapies was reported only for those who remained uncontrolled, but SSAs were the most common therapy in this group (alone in more than 15%, in combination with pegvisomant in about 10%, and in combination with DA in about 5%), followed by pegvisomant alone and DA alone²⁹. In the National Registry of acromegalic patients in Spain (REA), 42.3% of patients used pharmacologic treatment³⁰. In the most recent reporting period (2000–2009), SSAs were by far the most common, used in 76% of patients, followed by pegvisomant in 13.6%, and DA in 11.9%³⁰. In AcroBel, the Belgian registry on acromegaly, 78% of patients evaluated during 2003–2004 had used medical therapy at some time. Of these, 42% used SSA, 39% both DA and SSA, and 19% DA³¹.

What remains unclear and would be an interesting topic for further study are the clinical reasons for selecting a particular therapy in medication-naïve patients, as well as the choice of a DA over pegvisomant, or vice versa, in patients already on a SRL. The extent to which biochemical response, treatment tolerability, and cost affect the decision to select one medication over another also warrants further exploration.

An important limitation of this study was our inability to follow individual patients over a period of longer than 2–3 years as a result of disenrollment. This problem is common to all studies using insurance claims, but is particularly important in this condition. In acromegaly, recurrence requiring pharmacologic treatment peaks between 1–5 years after surgery but may occur up to 10 years later^{32,33}. Most of the patients we studied likely had surgery as their initial intervention, but we only began following them at the time of their first pharmacologic treatment. In addition, censoring at the end of enrollment meant we could not observe the end of therapy in most instances, making it impossible to draw conclusions about treatment duration. The use of registry-based data or electronic medical records could potentially address this issue in future research, as patients change providers much less frequently than they change insurance coverage.

Other limitations include the inclusion of only commercially insured patients; those with Medicare and the

uninsured were under-represented or not studied. We were unable to estimate the proportion with Medicare coverage using our data and found no studies of US that addressed this issue. However, a recent European registry study reported a mean age of 45 (interquartile range 35–55), suggesting a substantial majority of patients with acromegaly are <65 years old³⁰. The database lacked biochemical parameters, pathology results, and dosing for parenteral medications. Therefore, it could not be determined whether treatment changes were due to lack of response to therapy, disease progression, lack of clinical or biochemical control, serious side effects, prior therapy use not captured in the analytic database, or other reasons, whether appropriate or not. Finally, the study had small sample sizes for most individual treatment sequences of interest.

Conclusion

This study, which represents the largest claims-based analysis of acromegaly to date, used two claims databases across a 12 year period to examine complex treatment patterns in a difficult-to-study disease. Although wide variation in acromegaly treatment patterns exists in US clinical practice, in first-line, second-line, and third line therapy, SRL was the most commonly used drug class. A decline in the use of bromocriptine was noted during 2006–2013. Patients on first-line long-acting SRLs switched to combinations more often than to pegvisomant monotherapy and there was a wide variation in drug combinations used. The extent of switching between different monotherapies and varied use of drugs in combination in the time period studied may suggest an unmet need for alternative treatment options. Our technique of examining treatment patterns by combining claims databases may be used for other rare diseases. Chart reviews or other methodologies may be used to confirm and validate the utility of this technique.

Transparency

Declaration of funding

Funding for this study was provided by Novartis Pharmaceuticals Corporation.

Declaration of financial/other relationships

M.P.N. and W.H.L. have disclosed that they are employees of Novartis Pharmaceuticals Corporation. M.S.B. and E.C. have disclosed that they are employees of Partnership for Health Analytic Research LLC, a health services research company paid by Novartis to conduct this research. J.D.C., an associate professor of clinical medicine and co-director at the University of Southern California Pituitary Center, has disclosed that he consulted for Novartis.

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Notice of correction

Please note that Figure 2 has been corrected since the article was first published online (5 January 2016).