Acromegaly Clinical Trial Methodology Impact on Reported Biochemical Efficacy Rates of Somatostatin Receptor Ligand Treatments: A Meta-Analysis

John D. Carmichael, Vivien S. Bonert, Miriam Nuño, Diana Ly, and Shlomo Melmed

Pituitary Center (J.D.C., V.S.B., S.M.), Department of Medicine, and Department of Neurosurgery (M.N., D.L.), Cedars-Sinai Medical Center, Los Angeles, California 90048

Introduction: Biochemical efficacy of somatostatin receptor ligand (SRL) treatment in acromegaly is defined by metrics for GH and IGF-1 control. Since the earliest therapeutic trials, biochemical control criteria, medical formulations, and assay techniques have evolved.

Materials and Methods: We searched PubMed for English-language trials published from 1974 to 2012 evaluating 10 or more patients, with a duration of more than 3 months and biochemical control as a key objective. We used a random-effects model to compare biochemical outcomes for octreotide and lanreotide trials according to study design characteristics.

Results: A total of 4464 patients were enrolled in the analyzed trials; 4125 were treated, and 3787 completed study treatment. Overall achieved control rates were 56% for mean GH and 55% for IGF-1 normalization. Treatment duration was significantly related to both GH (P < .001) and IGF-1 control (P = .02). Prior SRL therapy (P = .01), and year of study publication (P = .03) were related to biochemical control for GH but not IGF-1. No statistically significant differences in GH or IGF-1 response rates were observed for multicenter vs single center, retrospective vs prospective, study drug, and preselection for SRL responsiveness. Dosing scheme, GH response criterion, or switch study design were also not statistically significant in determining GH or IGF-1 response rate.

Conclusions: Clinical design characteristics anticipated to impart efficacy bias including switching, preselection for SRL responsiveness, and retrospective design had no statistically significant impact on efficacy determination. Later year of publication, study duration, and prior SRL use are significant efficacy determinants for acromegaly trial outcomes. (J Clin Endocrinol Metab 99: 1825–1833, 2014)

Acromegaly is a rare disease caused by excess GH secretion, usually derived from a pituitary adenoma (1, 2). Uncontrolled acromegaly is associated with a 2- to 3-fold increase in mortality, compared with matched controls, with death arising mainly from cardiovascular, cerebrovascular, and respiratory causes (3). The goals of acromegaly therapy include reduction of serum GH and IGF-1 levels, shrinkage or removal of tumor mass, preservation of normal pituitary function, and amelioration of symptoms caused by excess GH and IGF-1, coinciding with reduced mortality rates (4). Surgery is considered the initial treatment of choice, especially for microadenomas, which have a higher remission rate than macroadenomas with or without invasive tumor extension (5, 6). Many patients are not cured by surgery; hence, multimodal adjunctive therapy is routinely necessary, with medical treatment and radiation therapy commonly used after surgery. Primary medical therapy is also appropriately indicated in some patients (7).

Somatostatin receptor ligand (SRL) medications have become a mainstay of therapy in the treatment of acromegaly since their initial introduction approximately 30

Abbreviations: Q, quartile; SRL, somatostatin receptor ligand.
years ago (8–10). Clinical trials have demonstrated biochemical control with attenuated serum GH and IGF-1 levels, reduced tumor size, and improved acromegaly symptoms. Both short-acting and long-acting preparations have been developed, with the earliest trials demonstrating effectiveness of octreotide, a small peptide with predominately somatostatin receptor subtype 2 activity (11, 12). Longer-acting preparations of octreotide (Octreotide LAR) and a second somatostatin receptor ligand medication, lanreotide (Lanreotide SR) subsequently also proved efficacious (13, 14). Lanreotide was formulated as a longer acting depot or autogel formulation, and subsequent clinical trials demonstrated biochemical effectiveness using a monthly dosage and then with every 6- to 8-week dosing in some patients, using the highest available dose of long-acting lanreotide (15).

Results of clinical trials evaluating biochemical efficacy have varied during the approximately 30 years of publication of these trials (16). The first reports of acromegaly treatment with somatostatin receptor ligand medication showed suppression of GH in response to single doses of octreotide (then SMS 201–995), with prolonged suppression without GH rebound, and reduction in IGF-1 (previously somatomedin-C) (17, 18). Over the ensuing years, clinical trials were conducted using varying study methodologies, large and small cohort sizes, short- and long-acting formulations of both octreotide and lanreotide brands, and varying durations of treatment. Serum hormone assay methodology also advanced, and sensitivity cutoff points used to establish disease control, for GH in particular, have decreased (19). Methods for measuring IGF-1 also advanced, with a need for more uniformity among commercial laboratories being recently emphasized (20, 21). However, a large degree of variation in IGF-1 results has limited the reliability of this test, even with more modern techniques (22).

Wide variations in clinical trial methods and design have hampered direct comparison of drug efficacy. Accordingly, the overall efficacy of these drugs is difficult to assess from the current body of literature. Disparate trial results coupled with varying study design elements make it challenging to establish a true estimate of efficacy for each drug. We sought to identify whether these design elements significantly determine individual efficacy rates for SRL therapies. To this end, we conducted a meta-analysis of studies and investigated relationships between study design elements and the reported biochemical response rates to SRL therapy.

Materials and Methods

We searched PubMed for acromegaly clinical trials published through December 2012 in the English language and evaluated treatment of acromegaly with SRLs. Studies were included if they reported data on treatment of at least 3 months’ duration and biochemical efficacy based on measurement of serum GH or IGF-1 levels as a key study end point. All trials must have reported a percentage of patients normalizing serum GH and/or IGF-1 levels. Case reports and case series were excluded, as were studies reporting fewer than 10 subjects. Studies that reported combined medical therapy in which individual cohorts of SRL monotherapy could not be identified were excluded. Bibliographies of previously published systematic reviews and meta-analyses were also reviewed for additional papers (16, 23, 24). Each manuscript was analyzed for a reported outcome response rate for GH and IGF-1 stated as a percentage of patients controlled by medical therapy. When cohorts of patients were identified within studies with distinct response rates, these cohorts were analyzed as substudies, as long as data were not duplicated.

Retrospective and prospective studies of both short- and long-acting octreotide and lanreotide formulations, both sustained-release and depot/autogel formulations, as primary or adjuvant therapy were included. Tumor shrinkage data were not analyzed because these data were recently reported in a separate meta-analysis (25). Individual studies were evaluated for study design, duration of study treatment, baseline demographic information, and clinical characteristics of subjects and for prior treatment with surgery, radiation, or medical therapy. SRL formulation and dosing, GH and IGF-1 assay methodology and biochemical control cutoff points used were extracted using methodology described in Supplemental Table 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org. The number of subjects treated was used as the primary data point to establish the overall number of subjects analyzed.

Criteria for GH and IGF-1 response were established by each individual study, and these criteria were used in this study to designate response to therapy. Studies often reported multiple response rates for different cutoff points within each study. All cutoff points reported by each study were recorded and analyzed separately. However, for the primary analysis, when multiple cutoff points were reported for the same cohort, a GH cutoff point of 2.5 μg/L was used preferentially for uniformity.

Statistical analysis

Abstracts from electronic search results were screened for potential acceptability. Full manuscripts were reviewed and data uniformly collected based on criteria decided on a priori (Supplemental Table 1). One reader then verified all data.

The main outcomes of interest were the percentage of patients with normal GH and/or IGF-1, and these were treated as equal primary end points of this study. Criteria were analyzed in relation to the percentage of patients with controlled GH, normal IGF-1, and composite response rates, if used. Differences in GH and IGF-1 response rates between designated cohorts were conducted using single factor random-effects models (one sided evaluations). Given the large heterogeneity among studies selected for this analysis, a random effects model takes into consideration varying effect size and sampling variability of experimental units (ie, subjects) into studies. Overall average treatment effects by study-specific factors including study type and size, dosing method, and preselection of subjects for SRL responsiveness were conducted using the random-effects model. Assessment of study heterogeneity was performed by visual inspection of GH and IGF-1 response rates across the studies included in this anal-
Averages, medians, interquartile ranges, 95% confidence intervals (CIs), and P values were reported throughout. A value of \( P < 0.05 \) was considered to be statistically significant. All statistical analyses were conducted in SAS version 9.2 (SAS Institute).

Results

Study selection

The process of study selection is depicted in Figure 1. Initial electronic search criteria yielded 577 papers that were screened. Ultimately, 79 publications with 90 analyzable cohorts were identified to qualify for comparative analysis (see Supplemental References) (Table 1 and Supplemental Table 2).

Study and patient characteristics

Eligible studies were published between 1987 and 2012 and were retrospective (24%), prospective (76%), multi-center (46%), and single-center (54%) studies. Thirty-seven percent included treatment with lanreotide, 59% octreotide, and 4% reported data for cohorts treated with either drug. Among octreotide trials, 36% were short-acting octreotide (OCT-SQ), and 64% long-acting repeatable (OCT-LAR). Lanreotide sustained release (LAN-SR) was represented in 52% and autogel/depot formulation (LAN-ATG) in 49%. Preselection for favorable treatment response was reported in 33% of trials, 14% were switch studies, and 60% included patients with previous SRL therapy. A short octreotide test to assess responsiveness to SRL therapy was used in 29% of trials. Median dosing duration was 12 months with 57% of studies reporting a titrated dosing scheme, 13% fixed dose, and 30% fixed dose followed by titration. Forty-three percent of studies used a GH cutoff value less than 2.5 \( \mu \text{g/L} \), whereas 44% used a cutoff point of 2.5 \( \mu \text{g/L} \) and 12% a cutoff point greater than 2.5 \( \mu \text{g/L} \). Some studies reported more than one cutoff point (Table 2).

A total of 4,464 patients were enrolled in the analyzed trials; 4125 were treated, and 3787 completed study treatment (Table 1). The mean age of patients was 50.6 years.

Biochemical control

The average GH control rate was 56% and 55% for IGF-1 normalization (Table 3). There was a high degree of variability in reported GH and IGF-1 response rates (Figure 2, A and B, and Supplemental Table 2). GH and IGF-1 response rates moderately correlated (\( r = 0.492; \ P < 0.001 \)). Treatment with any lanreotide formulation yielded a GH response rate of 59% and an IGF-1 response rate of 53%. Octreotide treatment with all formulations yielded a GH response rate of 55% and an IGF-1 response rate of 56%. No significant difference in treatment response was found between these two drugs with respect to GH (\( P = .37 \)) and IGF-1 control (\( P = .46 \)). Similarly, no GH (\( P = .3 \)) or IGF-1 (\( P = .23 \)) response differences were found for the long-acting SRL preparations (Table 3).

Relationships between study methodology and biochemical response

Longer duration of SRL therapy reported within the study, independent of any prestudy treatment, was related to higher GH response rate (\( P < .001 \)) and IGF-1 response rate (\( P = .02 \)) (Table 4). Individually, treatment with fixed, titrated, or fixed-then-titrated dosing schemes did not significantly affect GH or IGF-1 response. However, when fixed dosing alone was compared with titrated and fixed-then-titrated studies combined, the difference ap-
proached statistical significance for GH (titrated: 57.3% ± 19.2% vs fixed: 46.1% ± 21%; \( P = .06 \)). IGF-1 was not statistically different for response rate: (titrated: 55.3% ± 16.7% vs fixed: 49.5% ± 21%; \( P = .36 \)). No other study parameters had a statistically significant relationship with both GH and IGF-1 outcomes. When analyzing studies that allowed for a treatment period of 12 months or greater, there was a difference in efficacy rate for GH response (12 months, \( n = 44 \): 50.3% ± 21.4% vs ≥12 months, \( n = 46 \): 61.5% ± 16.1%; \( P = .01 \)), but the difference in IGF-1 response was not significant (12 months: 52.4% ± 19% vs 56.6% ± 15.5%; \( P = .16 \)).

Prior SRL therapy (\( P = .02 \)), and year of study publication (\( P = .03 \)) were related to higher biochemical control for GH but not for IGF-1 (Table 5). The percentage of patients included in the studies that comprised SRL therapy-naïve subjects was inversely related to GH response rates (\( P = .03 \)) but not to IGF-1 responses. When studies published two response rates for different GH cutoff points, results were substituted and the entire data set reanalyzed. Relationships to duration of study (\( P = .003 \)) and year of study (\( P = .02 \)) remained significant. No other variable was significantly related to GH response rate.

To analyze changes in study design over time, we divided the studies into quartiles by year published. Number of subjects per study or median age of subjects did not change over the time frame studied. The percentage of

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**Table 1. Study and Treatment Characteristics of 90 Eligible Trials Included in Analysis**

| Variables                              | All Studies (n = 90) |
|----------------------------------------|----------------------|
| Total number of patients               | 4464                 |
| Accrued                                | 4125                 |
| Completed                              | 3787                 |
| Age, y                                 | Mean (SD) 50.6 (4.9) |
| Median (IQR)                           | 48 (53)              |
| Missing, n (%)                         | 12 (13.3)            |
| Study type, n (%)                      | Retrospective 22 (24.4) |
| Prospective                            | 68 (75.6)            |
| Multicenter                            | 41 (45.6)            |
| Single-center                          | 49 (54.4)            |
| Treatment type, n (%)                  | Lanreotide 33 (36.7) |
| Octreotide                             | 53 (58.9)            |
| Other (ie, both)                       | 4 (4.4)              |
| Treatment arms, n (%)                  | Lanreotide ATG 16 (48.5) |
| Lanreotide SR                           | 17 (51.5)            |
| Octreotide LAR                         | 34 (64.2)            |
| Octreotide SC                           | 19 (35.9)            |
| Treatment duration, mo                 | Mean (SD) 15.1 (12.6) |
| Median (IQR)                           | 12 (6–18)            |
| Dosing scheme, n (%)                   | Titrated 27 (30)     |
| Fixed                                  | 12 (13.3)            |
| Fixed/titrated                         |                     |
| Year of study, n (%)                   | 1987–1989 4 (3.9)    |
| 1990–1999                              | 30 (29.1)            |
| 2000–2009                              | 56 (53.4)            |
| 2010–2012                              | 13 (12.6)            |
| Treatment-naïve patients, %            | Mean (SD) 38 (39)    |
| Median (IQR)                           | 24 (0–70)            |
| SRL-naïve patients, %                  | Mean (SD) 58 (43)    |
| Median (IQR)                           | 68 (8–100)           |
| Prior surgery, %                       | Mean (SD) 45 (32)    |
| Median (IQR)                           | 52 (0–63)            |
| Prior radiotherapy, %                  | Mean (SD) 20 (20)    |
| Median (IQR)                           | 18 (0–33)            |
| Short octreotide test, n (%)           | Yes 26 (29)          |
| No                                     | 64 (71)              |
| Switch study, n (%)                    | Yes 13 (14)          |
| No                                     | 76 (84)              |
| Undetermined                           | 1 (1)                |
| Prior SRL therapy, n (%)               | Yes 54 (60)          |
| No                                     | 33 (37)              |
| Undetermined                           | 3 (3)                |
| Preselection favorable, n (%)          | Yes 29 (32)          |
| No                                     | 59 (66)              |
| Undetermined                           | 2 (2)                |

Abbreviation: IQR, interquartile range.

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**Table 2. Frequency of GH Cutoff Criteria Used by Each Study**

| GH Cutoff Point, ng/mL | n  | Method of GH Measurement |
|------------------------|----|--------------------------|
| 0.38                   | 2  | Random: n = 2            |
| 1.00                   | 14 | Mean: n = 6              |
| 1.9                    | 5  | OGTT: n = 5              |
| 2                      | 17 | Random: n = 1            |
| 2.50                   | 42 | Mean: n = 31             |
| 4                      | 2  | Random: n = 5            |
| 4.6                    | 2  | Mean: n = 2              |
| 5                      | 12 | Mean: n = 10             |
| Not reported: n = 2    |    | Basal/fasting: n = 3     |
| Prior SRL therapy (\( P = .02 \)), and year of study publication (\( P = .03 \)) were related to higher biochemical control for GH but not for IGF-1 (Table 5). The percentage of patients included in the studies that comprised SRL therapy-naïve subjects was inversely related to GH response rates (\( P = .03 \)) but not to IGF-1 responses.

When studies published two response rates for different GH cutoff points, results were substituted and the entire data set reanalyzed. Relationships to duration of study (\( P = .003 \)) and year of study (\( P = .02 \)) remained significant. No other variable was significantly related to GH response rate.

To analyze changes in study design over time, we divided the studies into quartiles by year published. Number of subjects per study or median age of subjects did not change over the time frame studied. The percentage of

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retrospective studies increased over the 25 years analyzed (9%, 21%, 20%, and 48% in quartiles Q1, Q2, Q3, and Q4, respectively) but did not achieve statistical significance ($P = .06$), whereas the percentage of multicenter studies or single-center studies did not significantly change. Use of a composite end point (control of both GH and IGF-1) increased over time: (13%, 21%, 60%, and 70% in Q1, Q2, Q3, and Q4, respectively). When studies reported a composite end point, the mean difference between the composite and individual GH and IGF-1 efficacy rates were 13% ± 14.5% and 8% ± 9.3%, respectively.

**Discussion**

This acromegaly meta-analysis reports efficacy rates for biochemical control of GH and IGF-1 levels derived from 90 treated cohorts from 79 publications. Based on our results, very few study methods or variations in design had significantly measurable impact on GH or IGF-1 response rates. We found no significant difference between SRL type both when combining shorter- and longer-acting medications or when separately evaluating the currently commercially available long-acting formulations.

The overall efficacy response rate for SRL therapy derived from these cohorts is 56% for GH control (as defined by each individual study) and 55% for IGF-1 normalization with a high degree of variation among all studies. In many ways, the studies were not uniform in their approach to assessing efficacy of SRL therapy. Rather than include only studies that uniformly could be compared with each other (an approach that effectively would have eliminated many published clinical trials), we sought to include as many studies as possible to allow comprehensive analysis of factors that may have a role in influencing biochemical efficacy. We hypothesized that baseline patient characteristics, study design aspects such as inclusion/exclusion criteria, duration of therapy, and methods of assessment of biochemical efficacy would have a significant effect on biochemical control rates for each study.

An adequately powered, randomized trial comparing lanreotide to octreotide has never been performed. Two prior papers, using a systematic approach to the published literature, report on the analysis of several clinical trials of SRL therapy in acromegaly (23, 24). A meta-analysis of 44

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**Table 3. Outcome Response Rates for SRL Medications**

| Outcome                  | All Studies (n = 90) | LAN ATG (n = 16) | OCT LAR (n = 34) | $P$ Value |
|--------------------------|----------------------|------------------|------------------|-----------|
| GH response (%)          | Mean (SD)            | 56 (19.7)        | 64 (17.5)        | 58 (16.2) | .30       |
|                          | Median (IQR)         | 55 (44–69)       | 59 (49–78)       | 60 (45–70) |
|                          | Missing (%)          | 5 (5.6)          | 1 (6.3)          | 0 (0)     |
| IGF-1 normalization (%)  | Mean (SD)            | 55 (17.3)        | 61 (14.8)        | 55 (18.4) | .23       |
|                          | Median (IQR)         | 54 (42.5–65)     | 56 (51–64)       | 61 (36–66) |
|                          | Missing (%)          | 2 (2.2)          | 0 (0)            | 0 (0)     |

Abbreviations: IQR, interquartile range; LAN ATG, lanreotide autogel/depot; OCT LAR, octreotide long-acting repeatable.
clinical trials of octreotide and lanreotide published before the end of 2003 (23), comprised trials of greater than 3 months treatment duration, reporting biochemical data for at least five subjects. The analysis did not include the lanreotide autogel/depot formulation because it was not yet available. An important finding from this analysis was that when studies that preselected subjects for drug responsiveness were excluded, octreotide LAR had superior efficacy when compared with the lanreotide SR formulation in terms of IGF-1 normalization and GH control. In our analysis, the addition of the LAN-ATG formulation eliminates superiority of any one formulation. Importantly, our analysis demonstrates that preselection does not have a significant impact on therapeutic response rate.

### Table 4. Univariate Analysis of Factors Associated With GH and IGF-1 Response for 90 Eligible Studies (Effect Size)

| Variables                     | GH Effect Size   | 95% CI          | P Value | IGF-1 Effect Size | 95% CI          | P Value |
|-------------------------------|------------------|-----------------|---------|-------------------|-----------------|---------|
| Total number of patients      |                  |                 |         |                   |                 |         |
| Accrued                       | -0.02            | (-0.1, 0.06)    | .71     | -0.04             | (-0.12, 0.04)   | .31     |
| Treated                       | 0.002            | (-0.10, 0.10)   | .97     | -0.02             | (-0.1, 0.06)    | .62     |
| Completed                     | -0.02            | (-0.14, 0.10)   | .78     | -0.02             | (-0.12, 0.08)   | .69     |
| Dropout rate (%)              | 0.17             | (-0.10, 0.44)   | .47     | -0.11             | (-0.35, 0.13)   | .37     |
| Age, y                        | 0.12             | (-0.82, 1.06)   | .81     | 0.37              | (-0.45, 1.19)   | .39     |
| Year of study                 | 0.76             | (0.11, 1.41)    | .03     | -0.17             | (-0.78, 0.44)   | .59     |
| Baseline GH (n = 73)          | -0.07            | (-0.38, 0.24)   | .67     | 0.12              | (-0.13, 0.37)   | .37     |
| Baseline IGF-1 (n = 55)       | -0.03            | (-1.70, 1.64)   | .97     | -0.02             | (-2.18, 2.14)   | .98     |
| Dose duration, mo             | 0.57             | (0.24, 0.90)    | .001    | 0.35              | (0.06, 0.64)    | .02     |
| SRL therapy naïve, %          | -0.11            | (-0.21, -0.01)  | .03     | -0.04             | (-0.12, 0.04)   | .39     |
| TX naïve, %                   | -0.05            | (-0.17, 0.07)   | .44     | -0.04             | (-0.14, 0.06)   | .43     |

Abbreviations: CI, Confidence interval; TX, treatment.

### Table 5. Univariate Analysis of Factors Associated With GH and IGF-1 Response for 90 Eligible Studies

| Variables                     | Comparison of Response Rates |
|-------------------------------|------------------------------|
| GH, %                         | 95% CI                  | P Value | IGF-1, %         | 95% CI                  | P Value |
| Study type                    |                             |         |                   |                         |         |
| Retrospective                 | 56                          | (47, 66)| .88               | 54                      | (45, 62)| .84     |
| Prospective                   | 56                          | (51, 61)| .58               | 55                      | (51, 59)| 1.00    |
| Multicenter                   | 57                          | (49, 66)| .58               | 55                      | (47, 62)| .98     |
| Single center                 | 55                          | (49, 60)| .58               | 55                      | (50, 60)| .98     |
| Treatment type                |                             |         |                   |                         |         |
| Lantreotide                   | 59                          | (50, 68)| .37               | 53                      | (45, 61)| .46     |
| Octreotide                    | 55                          | (49, 60)| .37               | 56                      | (0, 61)| .12     |
| Preselection favorable        |                             |         |                   |                         |         |
| Yes                           | 61                          | (52, 70)| .09               | 59                      | (51, 67)| .12     |
| No                            | 53                          | (48, 58)| .09               | 53                      | (48, 57)| .12     |
| Prior SRL therapy             |                             |         |                   |                         |         |
| Yes                           | 64                          | (55, 72)| .01               | 57                      | (49, 64)| .41     |
| No                            | 52                          | (47, 57)| .01               | 54                      | (49, 58)| .41     |
| Switch study                  |                             |         |                   |                         |         |
| Yes                           | 63                          | (51, 75)| .18               | 60                      | (49, 70)| .29     |
| No                            | 54                          | (50, 59)| .18               | 54                      | (50, 58)| .29     |
| GH criteria                   |                             |         |                   |                         |         |
| <2.5                          | 56                          | (43, 70)| .94               | 56                      | (44, 68)| .75     |
| 2.5                           | 56                          | (43, 69)| .94               | 53                      | (41, 65)| .75     |
| >2.5                          | 54                          | (42, 66)| .94               | 54                      | (44, 65)| .75     |
| Titration scheme              |                             |         |                   |                         |         |
| Titrated                      | 55                          | (46, 65)| .10               | 54                      | (46, 62)| .40     |
| Fixed                         | 46                          | (32, 60)| .10               | 50                      | (37, 61)| .40     |
| Fixed/titrated                | 61                          | (54, 68)| .10               | 58                      | (51, 64)| .40     |
| SRL therapy naïve, %          |                             |         |                   |                         |         |
| 100% SRL Rx naïve             | 51                          | (38, 63)| .06               | 53                      | (43, 64)| .40     |
| 0% SRL Rx naïve               | 63                          | (53, 73)| .06               | 58                      | (49, 67)| .40     |

Abbreviations: CI, confidence interval; RX, therapy.

a Extremes (100% SRL Rx naïve: n = 38; 0% SRL Rx naïve: n = 20).
In contrast, the prior meta-analysis demonstrated an increased rate of normalization of IGF-1 but not of GH. Differences in these results may relate to the inclusion of later clinical trials, including more trials devoted to the investigation of longer acting formulations.

In 2008, a critical analysis of commercially available somatostatin analogs reported the biochemical efficacy of OCT-LAR, LAN-SR, and LAN-ATG (24) from aggregated findings of the largest studies available to date for SRL medications. It was noted that the methods of the clinical trials that were available at the time included features that could sway response rates of the various clinical trials, such as preselection of subjects, lack of ability to titrate dose during the study, and variable treatment duration in reported studies. It was concluded that variation in study design might explain differences noted in comparisons of different formulations of SRL therapy. It was also noted that few studies directly compared OCT-LAR with LAN-ATG and that all comprised small patient numbers. No significant differences in efficacy were found when comparing results for OCT-LAR and LAN-ATG. We found similar results when examining additional studies devoted to assessment of efficacy of these two agents. In contrast to the observations in the prior critical analysis (24), however, we found very few clinical trial methods that had a significant impact on response rates, including preselection of subjects and fixed or titrated dosing.

Methodology of clinical trials that did indeed impact reported efficacy outcomes in our study included the year the study was published, the duration of the treatment during the study, and treatment with SRL therapy prior to enrollment. Studies conducted later had a more favorable GH response rate than earlier studies. This seems counterintuitive as criteria for biochemical control evolved and became more rigorous over the years. Study design also did not explain these results because there was no outcome difference for prospective and retrospective design, despite more retrospective reports published in later years. We evaluated prior SRL therapy in several ways, and when evaluating differences between trials that included subsets with prior SRL therapy compared with those that did not, GH response was notably higher (64%) compared with those that recruited patients naïve to SRL therapy (52%) (P = .01). Many studies included a mix of subjects; however, a closer look at this question revealed a significant inverse relationship (P = .03) between the percentage of subjects enrolled who were SRL therapy naïve and subsequent GH responses. However, when comparing studies that included only 100% SRL-naïve (n = 38) and 0% SRL-naïve subjects (n = 20), the relationship did not achieve statistical significance (P = .06). Because prior therapy with SRL medications and biochemical outcome appear to be related, switch study designs could be expected to confer higher response rates. However, we did not find a statistically significant relationship between the outcome and this study design in our analysis.

Changes in methodology

It is generally accepted that retrospective studies, use of preselected patients, or patients who have been treated with SRL therapy prior to study entry would impart a higher rate of normalization of GH and IGF-1 levels. Although we did observe that prior use of SRL therapy was related to outcome, not all methods of testing this relationship maintained statistical significance. Surprisingly, retrospective studies did not exhibit higher response rates than prospective studies, and preselection also did not favor a higher therapeutic response rate.

Some methodology changes were apparent across studies included in this analysis. Notably, the use of a more stringent GH sensitivity cutoff point was used more frequently in recent studies. Similarly, the use of a composite response rate, in which subjects were reported as controlled when both IGF-1 normalization and a safe level of GH was attained, was published after this approach was emphasized in the consensus guidelines for the management of acromegaly (26).

Both criteria for disease control as well as assays used to measure GH and IGF-1 have changed over the years. The most notable change in GH measurement has been the change from early RIA to more modern immunometric assays, altering the way acromegaly patients are assessed in several ways. The first noticeable change in assay technology was that the newer immunometric assays are more specific to the 22-kDA GH isomer, at the expense of not measuring less common but potentially clinically meaningful GH isomers (27). This change has had a profound impact on the ability to measure lower serum levels of GH. Improved assay sensitivity enabled more accurate distinction of cured subjects from those not cured (28). Because these changes in assays affected clinical practice, they also affected the end points commonly used for clinical trials. In general, however, most clinical trials used a GH cutoff point of 2.5 ng/mL established by using a series mean of values. Lower cutoff points established in clinical practice and emphasized by updates in consensus statements regarding acromegaly management have not fully replaced more traditional cutoff points for GH, and the reasoning behind this is not entirely apparent (4). Often, lower biochemical cutoff points are published alongside higher cutoff points.

Although IGF-1 assays changed over the years, this did not have the dramatic effect that GH did in terms of generalizing results. The variability of IGF-1 assays has been
well characterized (22, 29). Because published studies have almost entirely used age-matched control data to establish a normal IGF-1 range, there is little perceptible effect of the assay changes during the time these trials have been conducted.

The wide variation in clinical trial design is evident from examination of the literature devoted to clinical trials evaluating SRL efficacy. Variation in dosing methods, entry criteria, assessment of biochemical control potentially play a role in determining how well a drug will control the enrolled subjects. We expected to find stronger relationships between methodological factors and reported drug efficacy rates. It is possible that an analysis devoted to methods of clinical trials does not fully capture the inter-individual variability inherent in characterizing a medication response. Only a disease registry, in which detailed assessments of the individual patients are available, would enable determining individual factors that confer medication effectiveness.

With the observed variability of biochemical outcomes across multiple studies, it becomes difficult to ascertain the true efficacy of SRL therapy in the treatment of acromegaly. This is important because different classes of drugs and their estimated efficacy rates to SRL medications are compared in an effort to best formulate a plan of care. Selection of therapy often depends on an estimate of how well the drug will work compared with other therapeutic options. For SRL therapy, the true overall biochemical efficacy rate is likely within a range surrounding the mean of 55%, but the size of that range is large and, based on this analysis, not related to many of the variables that underlie the clinical trials that comprise this body of data. At this time, predicting efficacy rates based on clinical trial design methods, patient characteristics, or drug formulations does not seem possible, aside from a few notable exceptions such as duration of therapy or exposure to prior SRL therapy. These trial design features have little to do with the individual variation that is not possible to discern with this analysis and not possible to predict for individual patients.

Acromegaly treatment has been shaped by periodic publication of clinical guidelines and consensus statements, based on evidence-based recommendations and clinical expertise of the participants. Just as methodology of clinical trials has changed over time, there have also been changes in the trends of acromegaly clinical care (30, 31). The data presented here should help define the expected response rate for somatostatin analogs and help clarify the debate regarding comparative efficacy rates between drug classes. This analysis brings to light and quantifies the variation in clinical trial design and the average response rate accrued from many years of clinical trials. The results shown here place into context how other medications compare with somatostatin analogs. However, wide variation in reported results demonstrates the imprecision of clinical trials in determining a true response rate for a unique drug or class of drugs used in a very rare disease.

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Address all correspondence and requests for reprints to: Shlomo Melmed, MD, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 2015, Los Angeles, CA 90048. E-mail: melmed@cshs.org.

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References

1. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest. 2009;119:3189–3202.
2. Ribeiro-Oliveira A, Barkan A. The changing face of acromegaly—advances in diagnosis and treatment. Nat Rev Endocrinol. 2012;8: 605–611.
3. Sherlock M, Ayuk J, Tomlinson JW, et al. Mortality in patients with pituitary disease. Endocr Rev. 2010;31:301–342.
4. Giustina A, Chanson P, Bronstein MD, et al. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab. 2010;95(7):3141– 3148.
5. Nomikos P, Buchfelder M, Fahlbusch R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical ‘cure.’ Eur J Endocrinol. 2005;152:379–387.
6. Jane JA, Starke RM, Elshobhy MA, et al. Endoscopic transphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. J Clin Endocrinol Metab. 2011;96:2732–2740.
7. Giustina A, Bronstein M, Casanueva FF, et al. Current management practices for acromegaly: an international survey. Pituitary. 2011;14:125–133.
8. Melmed S. Medical progress: acromegaly. N Engl J Med. 2006;355: 2558–2573.
9. Weckbecker G, Lewis I, Albert R, Schmid HA, Hoyer D, Bruns C. Opportunities in somatostatin research: biological, chemical and therapeutic aspects. Nat Rev Drug Discov. 2003;2:999–1017.
10. Fleseriu M, Delashaw JB, Cook DM. Acromegaly: a review of current medical therapy and new drugs on the horizon. Neurosurg Focus. 2010;29:E15.
11. Lamberts SW, Uitterlinden P, Verschoor L, van Dongen KJ, del Pozo E. Long-term treatment of acromegaly with the somatostatin analogue SMS 201–995. N Engl J Med. 1985;313:1576–1580.
12. Ezzat S, Snyder PJ, Young WF, et al. Octreotide treatment of acro-
megaly. A randomized, multicenter study. Ann Intern Med. 1992;117:711–718.

13. Caron P, Cogne M, Gushthi-Joudet B, Wakim S, Catus F, Bayard F. Intramuscular injections of slow-release lanreotide (BIM 23014) in acromegalic patients previously treated with continuous subcutaneous infusion of octreotide (SMS 201–995). Eur J Endocrinol. 1995;132:320–325.

14. Melmed S, Cook D, Schopohl J, Goth MI, Lam KS, Marek J. Rapid and sustained reduction of serum growth hormone and insulin-like growth factor-1 in patients with acromegaly receiving lanreotide Autogel therapy: a randomized, placebo-controlled, multicenter study with a 52 week open extension. Pituitary. 2010;13:18–28.

15. Schopohl J, Strasburger CJ, Caird D, et al. Efficacy and acceptability of lanreotide Autogel(R) 120 mg at different dose intervals in patients with acromegaly previously treated with octreotide LAR. Exp Clin Endocrinol Diabetes. 2011;119:156–162.

16. Carmichael JD, Bonert VS. Medical therapy: options and uses. Rev Endocr Metab Disord. 2008;9:71–81.

17. Lamberts SW, Oosterom R, Neufeld M, del Pozo E. The somatostatin analog SMS 201–995 induces long-acting inhibition of growth hormone secretion without rebound hypersecretion in acromegalic patients. J Clin Endocrinol Metab. 1985;60:1161–1165.

18. Plewe G, Beyer J, Krause U, Neufeld M, del Pozo E. Long-acting and selective suppression of growth hormone secretion by somatostatin analogue SMS 201–995 in acromegaly. Lancet. 1984;2:782–784.

19. Clemmons DR. Clinical laboratory indices in the treatment of acromegaly. Clin Chim Acta. 2011;412:403–409.

20. Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. Clin Chem. 2011;57:555–559.

21. Bidlingmaier M, Strasburger CJ. Growth hormone assays: current methodologies and their limitations. Pituitary. 2007;10:115–119.

22. Pokrajac A, Wark G, Ellis AR, Wear J, Wieringa GE, Trainer PJ. Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. Clin Endocrinol (Oxf). 2007;67:65–70.

23. Freda PU, Katzenelson L, van der Lely AJ, Reyes CM, Zhao S, Rubinowitz D. Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2005;90:4465–4473.

24. Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab. 2008;93:2957–2968.

25. Giustina A, Mazzotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. PLoS One. 2012;7:e36411.

26. Giustina A, Barkan A, Casanueva FF, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab. 2000;85:526–529.

27. Strasburger CJ. Laboratory assessment of GH. Growth Horm IGF Res. 1998;8(suppl A):41–46.

28. Freda PU, Post KD, Powell JS, Wardlaw SL. Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. J Clin Endocrinol Metab. 1998;83:3808–3816.

29. Milani D, Carmichael JD, Wellkowitz J, et al. Variability and reliability of single serum IGF-I measurements: impact on determining predictability of risk ratios in disease development. J Clin Endocrinol Metab. 2004;89:2271–2274.

30. Sesmilo G, Gaztambide S, Venegas E, et al. Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA). Pituitary. 2013;16:115–121.

31. Howlett TA, Willis D, Walker G, Wass JA, Trainer PJ, Acromegaly Register Study Group (UKAR-3). 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 (Oxf). 2013;79:689–699.