Low-Dose Allergen Immunotherapy (LDA) vs. Subcutaneous Injection Immunotherapy: A Comparative Study

by Diego Saporta, MD, FAAOA

Introduction

Immunotherapy (administered either by injections or sublingually) is a very old treatment modality. Noon and Curtis were already working with these treatments in the early 1900s.[1,2]

Administration of low-dose allergen immunotherapy (LDA) was first described by Dr. Leonard McEwen in England (at the time, it was called EPD, or enzyme potentiated desensitization). He published several papers between 1967 and 1987, including a double-blind, controlled study.[3–9]

The American EPD Society was founded in the US to study the treatment. This society conducted a large multicenter study from 1993 to 2000, involving practitioners from the US and Canada. This, the North American EPD Study, evaluated 10,372 patients. The results showed a "satisfactory" response rate of 76% (20% excellent, 30% very good, and 26% good).[10]

EPD became unavailable in the US in 2001. Soon afterward, Dr. W. A. Shrader developed a similar treatment that he called LDA.[11] LDA is now used by a relatively small number of practitioners (slightly over 100 MDs or NDs) in the US and Canada.[10] While it is expected that the number of practitioners who incorporate LDA into their practices will increase over time as information about this treatment is now being offered in some societies, it is not likely that LDA will ever be used as frequently as conventional immunotherapy, as it lacks the scientific background of conventional immunotherapy and it is not approved by the FDA.[12] As long as LDA remains a non-FDA-approved modality, it will most likely remain a "noncovered" service by traditional insurance companies. While McEwen and Shrader have published about this topic, there is not enough research about this treatment modality.[3–9,13,14] It is improbable that large prospective trials with a placebo group will ever be planned to evaluate efficacy of LDA. All these reasons will likely prevent wide acceptance of this treatment modality.

LDA was incorporated into the author's practice in 2009. As with any new treatment modality, the question was, is it as effective as the one already in use? More importantly, patients often ask this same question before making a decision.

In contrast with LDA, subcutaneous injection immunotherapy (SCIT) has been used in the author's practice for more than 20 years, and sublingual immunotherapy (SLIT) since 2003. When SLIT was incorporated, demonstrating efficacy and finding that it performed as well as SCIT was an important piece of information at the time of patient counseling.[15] For similar considerations the present study was planned with the objective of finding how LDA performs when compared with SCIT in order to properly advise patients when discussing treatment options. It was very obvious from the first few administrations that LDA was safe and effective, but this information is not enough to determine if its efficacy is similar to usual immunotherapy.

Methods

Allergy charts from patients either on SCIT or LDA were consecutively collected. Inclusion criteria were:

Patients of either sex, any age, with or without asthma, who had been receiving either treatment for a minimum of 1 year, and had completed the symptom scoring sheet.

Data were entered into spreadsheets, utilizing only pertinent information, including date of test, age, sex, asthma diagnosis, and symptom-scoring sheet information, therefore keeping all personal information confidential. After recording this information, spreadsheets were organized in columns corresponding to each one of the parameters to be analyzed.

The data were sent to a statistician for analysis. A chi-square test was used to determine whether the samples were significantly different from each other, and the ANOVA was then used to compare the average values.

Symptom Scoring Sheet

A symptom scoring sheet is a useful instrument to evaluate how an allergy patient is doing during treatment. Our symptom scoring sheet includes the following fields:

a. Twenty-five symptoms that include 4 symptoms of the Total Nasal Symptom Score (TNSS): sneezing, runny nose, nasal obstruction, and nasal itching, and 21

other symptoms that we consider important for the management of the allergic patient. The symptoms are scored on a scale of 1 to 5, where 1 is "mild" and 5 is "very severe." (0 implies that symptom is not present).

b. Peak Flow (PF) value is the numerical value obtained with a PF meter at the time of scoring. The PF value is very simple to obtain and yet a very useful tool for the evaluation of treatment results. We found that when immunotherapy is successful the PF value increases over time, even in nonasthmatic patients. When the patient is not responding to the treatment, the PF value does not increase or even decreases.[16]
c. Medications used: A similar 1–5 scoring system is used wherein 5 means that the medication is used daily and 1 that it is used up to 2 times per month. (0 implies that the medication is not being used). The purpose of evaluating medications is not to determine which medication works better but rather how much allergy medication the patient is using at the time of scoring. When treatment is successful, the medication score decreases.

With LDA, scoring is obtained each time treatment is administered. With SCIT, scoring is obtained approximately every 2 to 3 months.

The following parameters are obtained each time the scoring is done:

a. TNSS: This is the numerical value obtained by adding the scores given to the 4 symptoms described above. Maximal value of the TNSS is 20 (4 symptoms x 5).
b. Number of symptoms (#S): Total number of symptoms that the patient reports on each evaluation. This number includes all the symptoms present at the time of scoring. Maximal value for #S: 25.
c. Symptom score (SS): This is the numerical value obtained by adding the scores given to any of the 25 symptoms (therefore SS includes also the value of the TNSS). Maximal value for SS: 125 (25 symptoms × 5).
d. PF value: Numerical value determined when the patient is asked to use the PF meter.
e. Number of medications (#M): This is the number of medications that the patient is using at the time of scoring. The following medications are considered for assessment of patient's response to treatment:
    i. antihistamines
    ii. decongestants
    iii. leukotriene receptor blocker
    iv. intranasal steroids
    v. short-acting bronchodilators
    vi. inhaled corticosteroids (or combination inhaler)

    Maximal value for #M: 6.
f. Medication score (MS): This is the numerical value obtained by adding the scores given to medication use according to the 1–5 scale described above. The maximal value for MS: 30 (6 medications × 5. This implies that all medications are used daily).

Analysis

Both groups were evaluated before treatment initiation for age, gender, presence of asthma and for the values obtained from the symptom scoring sheet (TNSS, #S, SS, #M, MS, and PF).

The following determinations were planned:

1. a pretreatment evaluation with intergroup comparison.
2. scoring values at 12 months of treatment for each group.
3. intergroup comparison at 12 months.
4. scoring values at 24 months of treatment for each group.
5. intergroup comparison at 24 months.

Results were considered significant when $p < 0.05$.

Results

Each group (SCIT and LDA) had 52 charts. All patients received treatment for 12 months. At 24 months information was available only for 41 patients in the SCIT group and 32 patients in the LDA group. Eighteen patients in the LDA group had received SCIT prior to switching to LDA treatment. Significant results ($p < 0.05$) will be shown in bold.

Table 1: Demographics

	M/F	Total	Age ± SD	≤ 18 (%)	≤ 13 (%)	≤ 10 (%)	Asthma (%)
SCIT	23/29	52	45 ± 23	14 (26.9)	7 (13.5)	3 (6.0)	29 (55.8)
LDA	29/23	52	35 ± 20	13 (25.0)	12 (23.1)	11 (21.2)	31 (59.6)
			p < 0.05	N/S	N/S	**p < 0.05**	N/S

M/F: Male/Female
Age (SD): Age average ± standard deviation
≤ 18 (%): Number of children 18 years of age or younger (percentage from the total sample of 52)
≤ 13 (%): Number of children 13 years of age or younger (percentage from the total sample of 52)
≤ 10 (%): Number of children 10 years of age or younger (percentage from the total sample of 52)
Asthma (%): Number of patients who have asthma (percentage from the total sample of 52)
p: Probability
N/S: Not Significant

Table 1 shows the demographic information for both groups. ANOVA test shows that:

1. Mean patients age is lower in the LDA group ($p < 0.05$).
2. The number of children 18 years of age or younger is similar in both groups. When the children are subdivided by age there is a tendency for the children in the LDA group to be younger. In the subgroup of children 10 years of age or younger, this difference acquires significance ($p < 0.05$). The presence of more young children in the LDA group probably explains the significant age difference between both groups.
3. Asthma incidence in both groups is similar and has no statistical difference (N/S).

Pretreatment Evaluation

Evaluation of symptoms, medication use, and PF value was done for both groups before the beginning of treatment.

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Table 2. Pretreatment Evaluation

Pretreatment	SCIT	LDA	TS
TNSS	9.4 ± 5.8	9.1 ± 6.2	p = N/S
#S	11.7 ± 5.1	13 ± 5.3	p = N/S
SS	34.4 ± 20.1	38.1 ± 23.9	p = N/S
#M	1.73 ± 1.2	1.05 ± 1.1	**p < 0.01**
MS	6.15 ± 5.6	3.13 ± 3.8	**p = 0.01**
PF	354.4 ± 103.9	405.5 ± 154.4	p = N/S

Pretreatment: Scoring before treatment initiation
TNSS: Total Nasal Symptom Score
#S: Number of Symptoms
SS: Symptom Score
#M: Number of Medications
MS: Medications Score
PF: Peak Flow Value
All values ± Standard Deviation
SCIT: Subcutaneous Injection Immunotherapy
LDA: Low Dose Allergen Immunotherapy
TS: Test of significance
p: Probability
N/S: Not significant

Table 2 shows that the LDA group was taking fewer medications and medications were less frequently used than the SCIT group before treatment was started. Otherwise there were no other pretreatment differences between both groups.

Treatment Results for Each Group at 12 Months

Table 3: Treatment Results at 12 Months

12 mo/Pre	TNSS	#S	SS	#M	MS	PF
SCIT	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.01**	**p < 0.01**	**p < 0.05**
LDA	**p < 0.001**	**p < 0.01**	**p < 0.001**	N/S	**p < 0.05**	N/S

12 mo/Pre: Results at 12 months, compared with the pretreatment results.
TNSS: Total Nasal Symptom Score
#S: Number of Symptoms
SS: Symptom Score
#M: Number of Medications
MS: Medications Score
PF: Peak Flow Value
SCIT: Subcutaneous Injection Immunotherapy
LDA: Low Dose Allergen Immunotherapy
p: Probability
N/S: Not significant

Table 3 shows that both treatment modalities elicit a statistically significant improvement at 12 months of treatment in all parameters except #M and PF for the LDA group.

Intermodality Comparison at 12 Months

Table 4: SCIT vs. LDA 12-Month Treatment Results Comparison

TNSS	#S	SS	#M	MS	PF
p=0.73	p=0.09	p=0.67	p=0.06	p=0.08	**p < 0.05**
N/S	N/S	N/S	N/S	N/S	Yes SCIT

TNSS: Total Nasal Symptom Score
#S: Number of Symptoms
SS: Symptom Score
#M: Number of Medications
MS: Medications Score
PF: Peak Flow Value
SCIT: Subcutaneous Injection Immunotherapy
LDA: Low Dose Allergen Immunotherapy
p: Probability
N/S: Not significant

Table 4 shows that there are no differences in treatment results between groups at 12 months except for the PF value that appears to improve more with SCIT.

Treatment Results for Each Treatment Modality at 24 Months

Table 5: Treatment Results at 24 Months

24 mo/Pre	TNSS	#S	SS	#M	MS	PF
SCIT	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.01**	**p < 0.001**	**p < 0.05**
LDA	**p < 0.001**	**p < 0.05**	**p < 0.001**	**p < 0.05**	**p < 0.05**	N/S

24 mo/Pre: Results at 24 months are compared with the pretreatment scores
TNSS: Total Nasal Symptom Score
#S: Number of Symptoms
SS: Symptom Score
#M: Number of Medications
MS: Medications Score
PF: Peak Flow Value
SCIT: Subcutaneous Injection Immunotherapy
LDA: Low Dose Allergen Immunotherapy
p: Probability
N/S: Not significant

Table 5 shows that both treatment modalities elicit a statistically significant improvement at 24 months of treatment in all parameters except PF for LDA. The #M used in the LDA group, which did not decrease in a significant way at 12 months (Table 3), attained significance at 24 months.

Intermodality Comparison at 24 Months

Table 6: SCIT Vs. LDA 24-Month Treatment Results Comparison

TNSS	#S	SS	#M	MS	PF
p=0.75	p=0.43	p=0.8	p=0.44	p=0.25	p=0.32
N/S	N/S	N/S	N/S	N/S	N/S

TNSS: Total Nasal Symptom Score
#S: Number of Symptoms
SS: Symptom Score
#M: Number of Medications
MS: Medications Score
PF: Peak Flow Value
SCIT: Subcutaneous Injection Immunotherapy
LDA: Low Dose Allergen Immunotherapy
p: Probability
N/S: Not significant

Table 6 shows that at 24 months, the improvement in all parameters for both modalities is not statistically different. The difference in PF value improvement in favor of the SCIT group at 12 months (Table 4) disappeared at 24 months.

Conclusions

SCIT and LDA can be considered equivalent in reference to treatment results, even though LDA appears to require more time to attain the same results, at least in reference to the improvement of the PF value.

Discussion

This study showed that SCIT appeared to score better in 2 parameters: #M and PF (see Table 3), at least initially. As these differences disappeared over time, it could be hypothesized that if a study was done considering only results at longer treatment times (2 years or more), there would be no differences.

Bias?

The LDA group included a subgroup of 18 patients who received SCIT prior to initiation of LDA. These were patients who were not doing well on SCIT and opted to change into LDA. During study planning, it was not considered that prior treatment, even if failing, could have had an effect (partial improvement) on certain parameters. This could be the case for the PF value by prior administration of SCIT to these patients. Table 7 shows that when these 18 patients were enrolled in the LDA group their PF value had already improved by an average of 67 points.

Table 7: Effect of Prior SCIT on PF Value.

Prior SCIT (18 pts)	B4 SCIT	B4 LDA	Δ PF
AVG PF value	359	426	67 (N/S)

Prior SCIT (18 pts): Group of 18 patients who received SCIT prior to LDA
AVG PF value: Average PF value
B4 SCIT: Average PF value before SCIT was initiated (at enrollment)
B4 LDA: Average PF value before LDA was initiated (but after having received SCIT)
Δ PF: Average change in PF value
N/S: Not significant

Even though this is a nonsignificant improvement, it is likely a determining factor that prevents the PF value from attaining a statistically significant improvement in the LDA group (Tables 3 and 5), as more than 30% of the sample had already shown some improvement.

For the same reason it is likely that in the intermodality comparison at 12 months (Table 4), the PF value shows better results in the SCIT group, as the SCIT group included patients with the "full potential range" for improvement whereas the LDA group included more than 30% with "less potential range" for improvement. The fact that this difference disappeared over time (Table 6) suggests that ultimately the results of LDA treatment are as good as those of SCIT.

A similar reasoning could explain why the LDA group was using less medication at the beginning of the treatment (Table 2). In addition there are other considerations that could render the LDA group a biased sample. In other words, for the reasons explained below, the results in the LDA group may have favored worse outcomes:

1. Uninsured patients frequently choose LDA for economic reasons. It could be hypothesized that for the same reasons, these patients may not spend as much money on medications as insured patients. This could also contribute to the already discussed finding that the LDA group appeared to use fewer medications than the SCIT group. Potential for improvement (reduction in the number of medications used) is affected if the number used at the beginning of the trial is small. Maybe a larger sample would have overcome this difference.
2. LDA group included patients who were not improving on SCIT (and were switched to LDA). These previously treated patients may constitute a more complicated subgroup to treat. If these patients were left on SCIT it is possible that the final outcome of the group would have been worse. On the other hand, if before changing modalities these patients had partially improved, this would bias the LDA results (as discussed for the PF value).
3. There are potential problems in the way the symptoms are reported in the LDA group: By the nature of LDA, when LDA patients come for treatment they are often

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already symptomatic because at the beginning of treatment the effect lasts for only a few weeks. During this period, LDA administration is done once every 2 months.[11] It takes from 1 to 2 years for LDA patients to attain a more permanent improvement, and at that stage the administration of LDA becomes less frequent. With SCIT, once improvement develops it usually persists over time. This clearly tilts the scores of the LDA-treated group towards "worse outcome" because when symptoms were scored in this study, patients were often symptomatic again.

4. Some patients are so symptomatic that the consideration of SCIT is dangerous, as intradermal tests or shots have the chance to elicit severe reactions even with risk of life.[17,18] These difficult-to-treat patients may not attain the same level of improvement as less reactive patients. While this type of patient is not represented in the SCIT group, it can be represented in the LDA group as this is a safer treatment modality without risks for severe reactions and it is offered more liberally to those patients who are very reactive.
5. Patients with glycerin sensitivity may not have good results with conventional immunotherapy. They may not tolerate SCIT because of local arm reactions or they may not tolerate SLIT because of the glycerin used as diluent.[19] These patients are included in the LDA-treated group. If treated with conventional immunotherapy their treatment result scores could potentially tilt the SCIT-group scores towards worse outcome.

For all of the above reasons we think that this report is biased against the LDA-treated group. It is very likely that the results are tilted towards better scores in the SCIT-treated group and worse scores in the LDA-treated group. Despite this bias against LDA results, the outcome comparison of patients treated with SCIT or LDA is clearly the same. Therefore we strongly believe that expected results in patients treated with LDA should be at least as good as the ones expected by administering SCIT.

LDA has changed the way we approach the patients: when a patient has severe skin problems, oral allergy syndrome or other clear food issues, more and more we tend to favor administration of LDA as the most appropriate treatment modality (first line of therapy for these cases). In other words LDA has enabled us to successfully treat patients that either failed treatment or received no treatment before LDA was incorporated in our armamentarium. Despite the flaw in the study design and despite the potential bias against LDA, the results of this study are extremely encouraging and allow us to offer LDA as an effective and safe modality that can, without doubt compare to traditional immunotherapy.

Notes

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