The Effect of Zafirlukast (Accolate) on Early Capsular Contracture in the Primary Augmentation Patient: A Pilot Study

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Background: The development of capsular contracture following breast augmentation presents a challenge to the plastic surgeon. Treatment of capsular contracture with the leukotriene antagonist zafirlukast (Accolate, AstraZeneca, Wayne, PA) has received much attention in the media; however, there is limited proof of its effectiveness.

Objective: The purpose of this study was to prospectively examine a single surgeon’s experience using zafirlukast in the treatment of capsular contracture in primary, submuscular breast augmentation with saline-filled, smooth-walled implants.

Methods: Thirty-seven patients (74 breasts) who underwent primary submuscular breast augmentation with saline-filled, smooth-walled implants were evaluated at 1, 2, 4, 6, 12, 24, and 48 weeks postoperatively by 3 independent observers and rated for capsular contracture using a modification of the Baker classification. Patients who demonstrated any capsular contracture (higher than modified Baker 1.0) were offered off-label use of zafirlukast 20 mg PO BID for 3 or 6 months after full informed consent was reviewed and accepted. In addition, patients were offered liver function chemistries at the start of treatment and at 1, 3, and 6 months following zafirlukast treatment. The patients were assessed for implant mobility and capsular contracture at the initiation of leukotriene therapy and then again at 3- and 6-month time points.

Results: Forty-one breasts in this series (55.0%) were found to have early, mild capsular contracture. Specifically, 25 breasts were graded 1.5 (33.8% of total), 14 breasts graded 2.0 (18.9%), 1 breast graded 2.5 (1.4%), and 1 breast graded 3.0 (1.4%). Mean follow-up was 6.3 months. A positive response (complete or partial) was seen in a statistically significant proportion of treated breasts (75.7%, \( P < 0.05 \)). This response was maintained on a long-term basis, with a mean follow-up of 16.5 months.

Conclusions: Zafirlukast appears effective in treating early capsular contracture after primary submuscular breast augmentation using saline-filled, smooth-walled implants. Further prospective studies with control groups and long-term follow-up will be needed to address many unanswered questions, including whether leukotriene inhibitors have long-term effects on capsular contracture following breast augmentation. (Aesthetic Surg J 2005;25:26-30.)

Capsular contracture occurs at a rate of between 4.6% and 25% in the augmented breast. It is a problem that every aesthetic surgeon faces and would like to avoid. Numerous measures have been proposed and undertaken to prevent and/or reverse contracture, including meticulous hemostasis; perioperative antibiotics; pocket, intraluminal, or delayed intracapsular instillation of steroids and antibiotics; use of textured implants; subpectoral implant placement; breast massage, and capsulotomy or capsulectomy, all with varying success.

Although it appears that the process of capsular contracture is multifactorial, one common denominator in its successful treatment may be the abatement of inflammation. Triggers for inflammation, and in some cases development of capsular contracture, begin with the normal healing process. It is possible that the fluid retained around the breast implant following surgery causes ongoing inflammation. Now that the pathophysiology of contracture has been recognized, pharmacologic inhibition of the inflammatory process has become the major focus of research.

Leukotriene antagonists have recently emerged as effective prophylactic agents in reactive airway diseases. Anecdotal reports have indicated that zafirlukast (Accolate, AstraZeneca, Wayne, PA) was effective in the reversal of capsular contracture following breast augmentation, reportedly because of its inhibition of cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄), and its presumed suppressive effect on the myofibroblast, all of which are
presumed factors related to contracture. Thus far, the validity of such claims rests only on one suggestive case series of 5 patients. A more extensive study is warranted to determine the value of subsequent prospective randomized trials. We therefore present our experience with 37 patients (74 breasts) in a prospective pilot study that evaluated the use of zafirlukast in the treatment of early capsular contracture during a 13-month period.

**Materials and Methods**

**Patient selection**

Between December 2001 and January 2003, the senior author (LAC) performed 37 bilateral submuscular augmentation mammoplasties with saline-filled, smooth-walled breast implants (74 breasts). Patient ages ranged from 18 to 52 years (mean 34.8 years). Implant sizes ranged from 230 cc to 430 cc (mean 318 cc). All patients were placed on the same postoperative protocol, which included early implant mobility via self-massage once a day. Patients also received manual lymphatic drainage and deep tissue myofascial release by a physical therapist twice a week for 2 weeks, then once per week for 6 to 12 weeks. They also took vitamin E 400 IU orally twice daily starting at 4 weeks postoperatively. All patients had closed suction drains placed at the time of surgery, which were removed on the third postoperative day. The average drainage per breast for that period was >100 mL. This protocol has been used in the senior author’s practice for several years.

These patients were carefully followed-up at 1, 2, 4, 6, 12, 24, and 48 weeks postoperatively and evaluated for signs of infection, hematoma, and early capsular contracture (3 months or less postoperatively) by 3 independent observers (nursing staff, physical therapist, and the senior surgeon). The degree of capsular contracture was scored by using a modification of the Baker classification, as follows.

- Grade 1: Breast absolutely natural; augmentation undetectable
- Grade 1.5: Breast soft; implant detectable by physical examination
- Grade 2: Mild firmness; prosthesis not detectable by examiner or patient
- Grade 2.5: Mild firmness; implant detectable by examiner but not patient
- Grade 3: Breast moderately firm; implant detectable by patient
- Grade 4: Severe firmness, obvious from observation, with pain

Half integers were incorporated into the original grading system to account for clinical subtleties in the early contracture patient. Patients with any evidence of contracture (grade 1.5 or higher) were informed of the possible risks associated with the off-label use of zafirlukast. Once full informed consent was reviewed, patients were entered into the study. Only 2 patients of those who entered the study chose to have liver function studies followed; no changes in liver function were found.

**Zafirlukast regimen**

Patients who had modified Baker grade 1.5 or higher received zafirlukast 20 mg PO BID for a 6-month period or until contracture was completely reversed, whichever came first. Because of the well documented adverse effects of the agent, including liver failure and hepatitis, patients were offered hepatic profiles at 0, 3, and 6 months after beginning the regimen, as well as the ability to terminate the study at any time.

**Measurements**

Breasts were assessed at the start of the study and at 3-month and 6-month time points by 3 independent evaluators (nurse, physical therapist, senior surgeon) using the aforementioned grading system. Capsular contracture scores obtained in this manner were compared among the 3 different time points for each affected breast. Responses were scored as either complete (return to modified Baker grade 1), partial (reduction in capsular contracture index by 0.5), or nil (modified Baker grade the same or worse despite therapy). Those patients demonstrating a complete response to the study drug by 3 months after the beginning of treatment were removed from the protocol.

**Statistical analysis**

A comparison of the initial capsular contracture scores (baseline) with those at 3- and 6-months post-zafirlukast therapy was conducted using the Wilcoxon-signed rank test. Because our raw data was ordinal, and therefore could not be averaged, median values for 3 and 6 months were analyzed using smallest initial values and smallest 3-month values, respectively. Furthermore, because multiple tests were applied to the same data, the criteria for rejection of the null hypothesis had to be adjusted to avoid a Type I error. Therefore the criterion for rejection of the null hypothesis was $P < 0.05/4 = 0.0125$.

**Results**

Of the 37 bilateral procedures performed by the senior
author (74 breasts), 23 patients were positively screened for early capsular contracture (41 breasts, 55% of total). Stratification of these patients revealed the following: 25 breasts were graded 1.5 (33.8% of total), 14 breasts graded 2.0 (18.9%), and 1 breast graded 3.0 (1.4%) after 3 to 4 months (Table 1). Most patients enrolled in this study, therefore, had mild forms of early capsular contracture.

Examination of contracted breasts after only 3 months of zafirlukast therapy revealed a statistically significant reduction in contracture grades after 3 to 4 months (Table 2). Specifically, 22 out of 41 breasts (53.7%) demonstrated a complete response to zafirlukast therapy, whereas 9 (22.0%) demonstrated a partial response. The remaining 10 of 41 (24.3%) had no response (Figure 1, A). Cumulatively, a positive response (complete or partial) was evident in 75.7% of treated breasts. Multivariate analysis of left and right breasts revealed a median contracture grade of 1.0 in both breasts that was significant by Wilcoxon-signed rank test (Table 2). Two patients with bilateral contracture completely reversed by zafirlukast discontinued the drug at this time (4 breasts). When they returned for their 6-month evaluation, their grade had increased by 0.5. Zafirlukast treatments were restarted for a full 6-month course, with a full response occurring 6 to 9 months later. Of the remaining 37 breasts, 21 (56.8%) of the treated breasts demonstrated a complete response, 9 (24.3%) had a partial response, and 7 (18.9%) had no response (Figure 1, B). For the right breasts evaluated, statistical significance was maintained, whereas analysis of left breasts was only suggestive of a favorable treatment response. No patient during the course of the regimen had any untoward effects of the drug.

A critical standard for any treatment modality is its long-term beneficial effect. In our study, a long-term effect was maintained in the treated patients (Figure 1, C and Figure 2). When we examined the longevity of zafirlukast contracture reversal, we found that 30 of the total 41 breasts treated (73.1%) either maintained or improved to a modified grade 1.0 score, with a mean follow-up of 16.5 months (range 6-29 months) after the initiation of zafirlukast therapy (Figure 2). Only 7 out of 41 (17%) were modified grade 1.5, and 4 out of 41 (9.8%) (24.3%) had a partial response, and 7 (18.9%) had no response (Figure 1, B). For the right breasts evaluated, statistical significance was maintained, whereas analysis of left breasts was only suggestive of a favorable treatment response. No patient during the course of the regimen had any untoward effects of the drug.

![Figure 1. Response to zafirlukast in contracted breasts after (A) 3 months, (B) 6 months, and (C) long-term (mean follow-up, 16.5 months; range, 6-29 months). Complete, conversion to modified Baker grade 1.0; nil, no improvement or worsening grade; N, number of breasts.](image)

**Table 1. Stratification of breasts demonstrating contracture by modified Baker grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>N</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>25</td>
<td>33.8</td>
</tr>
<tr>
<td>2.0</td>
<td>14</td>
<td>18.9</td>
</tr>
<tr>
<td>2.5</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>3.0</td>
<td>1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

**Table 2. Modified Baker classification of capsular contracture in women treated for up to 6 months with zafirlukast for capsular contracture following breast augmentation**

<table>
<thead>
<tr>
<th>Breast (#)</th>
<th>Initial median grade (range)</th>
<th>Median grade after 3 months (range)</th>
<th>Median grade after 6 months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left breast (19)</td>
<td>1.5 (1-2.5)</td>
<td>1† (1.2)</td>
<td>1† (1.25)</td>
</tr>
<tr>
<td>Right breast (22)</td>
<td>1.5 (1-2.5)</td>
<td>1† (1-2)</td>
<td>1† (1.25)</td>
</tr>
</tbody>
</table>

*Twenty-three patients (41 breasts).
†Twenty-one patients (3 breasts) at 6 months of therapy; 2 patients who demonstrated a complete response to therapy at 3 months were removed from the protocol.
‡P < 0.05 versus initial grade by the Wilcoxon signed rank test, with the criterion for rejection of the null hypothesis corrected for multiple applications of the test to the same data.
were modified grade 2.0. These data were in stark contrast to our pre-treatment stratification analysis (Table 3) and further underline the potential long-term effect of a finite course of the leukotriene antagonist.

Discussion

Since the early reports of severe capsular contracture in the literature (reviewed in Embrey et al.13), various means have been tried to correct or prevent this disfiguring and even debilitating process. Even with the most definitive measure to eliminate contracture in the augmented breast (surgical intervention), capsulectomy bears a 79% success rate in recent series.13 Moreover, total capsulectomy of the submuscular pocket is technically challenging because of a relatively poorly defined tissue plane and the risk of muscle injury and/or pneumothorax.17 Open capsulotomy alone results in recurrence in up to 54% of cases.18 Secondary surgery is also not without potential complications, such as hematoma, infection, implant deflation and failure, breast asymmetry, and the need for further revision, and is an increased cost for the patient.

Our results in this pilot study point to a favorable response to the treatment of early capsular contracture with zafirlukast in patients who underwent primary submuscular augmentation with saline-filled, smooth-walled implants and took zafirlukast for at least 3 months. Overall, 75.7% of breasts receiving treatment had a complete or partial response to the leukotriene antagonist at 3 months, which was statistically significant for left and right sides. This response rate was maintained for 6 months (81.1%), as well for more than 1 year in follow-up (82.9%; mean 16.5 months). All enrolled patients tolerated the regimen well, with no untoward or deleterious effects.

Although these results support the use of zafirlukast in this setting, there are limitations to this study. First, the lack of a placebo-control arm makes any conclusion preliminary. It follows from this that the patients were not randomized, making this study susceptible to bias. However, observers blinded to unilaterality or bilaterality of contracture in patients allowed for an unbiased assessment of the effects of therapy. Another consequence of not having a control group is that confounding factors (massage, vitamin E) could not be assessed. It is possible that zafirlukast has an additive or synergistic effect with one or both of the other measures used to abate contracture in our practice. Further studies will determine these effects.

With respect to the therapeutic mechanism of leukotriene antagonism, we believe, as do others,11 that zafirlukast appears to modulate the immune system through its effects on cellular mediators involved in the inflammatory process (polymorphonuclear leukocytes [PMNs], macrophages, mast cells) as well as on the proposed culprit of the contractile process, the myofibroblast.19 Accordingly, leukotriene blockade would be effective early in the contracture process, when immune and inflammatory factors are still highly active. Our inclusion of early, mildly contracted breasts fits this theo-
ry, and this study represents the most comprehensive of its kind involving this subtype of contracture patients. We would not expect zafirlukast to be as effective in late, severe forms of contracture, although positive effects have been shown in a small case study.\(^{11}\) We propose that chemoprophylaxis or reversal of early, mild forms of contracture are appropriate indications for zafirlukast. For more severe forms of contracture (Baker 3 or 4), surgery may still be the intervention of choice.

**Conclusion**

Treatment of early, mild (modified Baker 1.5 to 2.5) capsular contracture with zafirlukast in the patient who undergoes primary submuscular breast augmentation with saline-filled, smooth-walled implants is supported by the results of this pilot study. It appears from these preliminary analyses that zafirlukast may be useful in this subpopulation of contracture patients. A prospective, randomized, double-blinded study involving such patients is warranted.

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**References**


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