Capsular contracture (CC) is one of the most frequent and troublesome complications of cosmetic breast augmentation. It is widely held that “newer generation” implants result in lower contracture rates than their predecessors. However, even with modern devices, there is a significant incidence of CC. Cumulative six-year data reported to the Food and Drug Administration (FDA) by Mentor Corporation revealed that 7.7% of patients receiving saline implants and 9.8% of patients receiving cohesive silicone gel implants for augmentation developed Baker III or IV contracture. Often, correction of CC requires reoperation. 

Leukotrienes—namely, LTC₄, LTD₄, and LTE₄—are implicated in the inflammatory cascade and have been postulated to be involved in the formation of CC. Therefore, leukotriene antagonists Accolate and Singular have been prescribed by plastic surgeons off-label to treat and prevent CC. To date, there are no studies investigating the efficacy of Singular on CC.

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Abstract

Background: Capsular contracture (CC) is one of the most common complications of breast augmentation surgery. Leukotrienes are implicated in the inflammatory cascade and have been postulated to be involved in the formation of CC. Therefore, leukotriene antagonists Accolate and Singular have been prescribed by plastic surgeons off-label to treat and prevent CC. To date, there are no studies investigating the efficacy of Singular on CC.

Objective: The authors retrospectively review a series of patients treated with Singular to determine whether it improves CC after breast implant surgery.

Methods: Nineteen patients treated with Singular by the senior surgeon (NH) after implant placement from March 2006 to November 2009 were included in this study. Follow-up on Singular efficacy was obtained by a combination of office chart review and standardized telephone questionnaire. Results were characterized as complete improvement, improvement, no change, or worse.

Results: Seventeen patients presented with CC resulting from a variety of breast operations. Two patients who had a history of recurrent CC were prescribed Singular prophylactically immediately after surgery. Twenty-one breasts with existing CC were included in the total. Two (11%) patients became worse, five (26%) improved, seven (37%) completely improved, and two (11%) were prevented from having CC formation.

Conclusion: Our preliminary study shows that Singular improves CC. Breasts with mild CC (Baker score < III) appeared to have better improvement with Singular compared to those with more severe contracture (Baker score III and IV). Singular is well tolerated with minimal side effects and can be administered to patients after breast implant surgery to improve CC.

Keywords
capsular contracture, Singular, breast augmentation, breast implants, complications

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Most research on the efficacy of leukotriene antagonists has been with Accolate. Two recent studies in a rat model showed that administration of Accolate in the presence of textured silicone implants resulted in a statistically significant decrease in mean capsule thickness when compared to controls.11,12 There was, however, no difference in capsule thickness with smooth implants.12 In a prospective study that measured mammary compliance, Scuder et al13 found an increase in breast compliance of up to 24% after six months in patients treated with Accolate compared to controls. In another study, Reid et al14 found that 55% of patients with CC had complete resolution of symptoms and 24% had partial reduction of symptoms after taking Accolate for six months.

In recent years, however, the use of Accolate has largely been abandoned because of potential adverse effects on the liver. In 2003, Gryskiewicz9,15 described 867 adverse events reported by the Center for Drug Evaluation and Research, including 66 cases of hepatitis or liver failure (two requiring liver transplants) and 12 deaths. His editorial in Plastic and Reconstructive Surgery recommended strongly against the use of Accolate because of these potentially harmful side effects.15 As a consequence, Singulair has become popular as an alternative leukotriene antagonist for treatment of CC. However, there are no published studies investigating the efficacy of Singulair in treating or preventing CC.

METHODS

This study included 19 breast implant recipients treated with Singulair by the senior surgeon (NH) between March 2006 and November 2009; 17 of these patients presented to the clinic with CC and two were treated prophylactically because of a history of CC. Four of the 17 patients with CC had bilateral contracture, for a total of 21 breasts treated for existing CC (defined as Baker score II or greater). All patients were informed of possible risks associated with the off-label application of Singulair. Patients were prescribed 10 mg of Singulair for 90 days and instructed to massage their breasts twice daily.

Follow-up of patient compliance and treatment results was obtained by a combination of chart review and a standardized telephone questionnaire. Patient race and age were noted, along with the indication for surgery and previous breast implant history. Implant size, type, position (submammary vs subpectoral), and operative incision were recorded. Breast firmness was assessed by the senior surgeon (NH) according to the Baker classification. The time interval from implantation to contracture was determined, as was the time that elapsed between development of contracture and initiation of Singulair treatment. It was also noted whether patients had subsequent revision surgery. Telephone interviews were used to determine the actual duration and dose of Singulair taken by the patient and whether the patient noted improvement, no change, or worsening of contracture.

Statistical analysis was performed by the UCLA Department of Biomathematics. Improvement was analyzed with the Wilcoxon signed rank test. To assess whether Baker grade affected response, each breast (n = 21) was placed into a “low Baker score” group (score greater than I and less than or equal to II) or a “high Baker score” group (score III or IV). Outcome of the treatments was assigned as follows: 0 = worsened, 1 = no change, 2 = improved, and 3 = completely resolved. The nonparametric Kruskal-Wallis test for ordered outcome determined whether implant position (submammary vs subpectoral) had any statistical correlation.

RESULTS

From March 2006 to November 2008, the senior author selected 19 patients (21 breasts) who presented with CC for treatment with Singulair. Two patients who had a history of recurrent CC were given Singulair prophylactically immediately after surgery. Follow-up ranged from five to 36 months (mean, 19 months).

The mean patient age was 44.2 years. Three patients were Hispanic and 16 were Caucasian. Those patients treated for established contracture had undergone a variety of procedures. Two patients had primary augmentation with mastopexy, one patient had breast reconstruction with implants for asymmetry after melanoma excision, four patients had an implant exchange, two had capsulotomy to revise the breast implant pocket, and the remaining 10 had secondary revision surgery with capsulectomy (Table 1). Of the 10 patients undergoing revision surgery, four had bilateral silicone implant rupture. Eleven of the patients had undergone previous breast revision.

All of the patients except one had Mentor memory gel smooth implants; the additional patient had a Mentor saline implant. The senior author inserted all of the original implants. Twelve patients had moderate-profile silicone implants and six patients had high-profile implants. The average volume was 450 cc. Six patients had their implants placed subpectorally and 13 had them placed in the submammary plane. CC occurred from 10 to 472 days postoperatively (mean, 162 days). A regimen of Singulair was begun immediately upon detection of CC in 16 patients; one patient had CC for 8.5 months before beginning Singulair treatment and two patients used it immediately after surgery prophylactically.

Our follow-up data showed that in two (11%) patients, the CC worsened, three (16%) patients had no change, five (26%) improved, and seven (37%) completely resolved. The two (11%) patients who received Singulair prophylactically were prevented from developing CC (Table 2). The four patients who had bilateral CC had the same results bilaterally. Of those four, two patients had no change in both breasts, one patient improved, and one patient worsened. Based on the assumption that CC does not improve without treatment,16 Singulair significantly improved CC (P < .05). Of the 12 patients who had improvement of their contracture, eight patients noticed improvement within days. Three patients reported that a month elapsed until they noticed improvement and one patient reported improvement after two months. Five patients had revision surgery that involved capsulectomy...
Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Race</th>
<th>Indication</th>
<th>Previous Surgeries</th>
<th>Size</th>
<th>Incision</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>W</td>
<td>D2—B complete capsulectomy, submam to subpec</td>
<td>1981—primary aug</td>
<td>B—Mentor MP 250 cc</td>
<td>Periareolar</td>
<td>Subpec</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>W</td>
<td>D2—B complete capsulectomy, submam to subpec</td>
<td>1991—primary aug, 2002 capsulectomy, RR</td>
<td>B—Mentor saline 250 cc</td>
<td>Periareolar</td>
<td>Subpec</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>H</td>
<td>A—crescent mastopexy and aug</td>
<td>None</td>
<td>B—Mentor MP 500 cc</td>
<td>Crescent mastopexy</td>
<td>Subpec</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>H</td>
<td>A—Binelli and aug</td>
<td>None</td>
<td>B—Mentor MP 400 cc</td>
<td>Binelli</td>
<td>Submam</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>W</td>
<td>D—sec rev bilateral complete capsulectomy</td>
<td>2004—primary aug</td>
<td>B—Mentor MP 550 cc</td>
<td>Periareolar</td>
<td>Submam</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>W</td>
<td>D—sec rev bilateral complete capsulectomy</td>
<td>1988—2005 8-10 RR for capsular contracture</td>
<td>B—Mentor MP 375 cc</td>
<td>Inframammary</td>
<td>Submam</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>W</td>
<td>B—implant exchange, submam to subpec</td>
<td>1994—primary aug, 2005 RR</td>
<td>B—Mentor HP 450 cc</td>
<td>Periareolar</td>
<td>Submam</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>W</td>
<td>D—sec rev B complete capsulectomy, subpec to submam</td>
<td>1984—primary aug, 2001 RR, 2007 RR</td>
<td>B—Mentor HP 700 cc</td>
<td>Crescent mastopexy</td>
<td>Submam</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>W</td>
<td>D2—B complete capsulectomy</td>
<td>1980s—2007 multiple RR and mastopexy</td>
<td>R—Mentor MP 300 cc</td>
<td>Vertical mastopexy</td>
<td>Submam</td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>W</td>
<td>C—capsulotomy</td>
<td>1998—primary aug, 2007 RR</td>
<td>B—Mentor HP 350 cc</td>
<td>Inframammary</td>
<td>Subpec</td>
</tr>
<tr>
<td>15</td>
<td>46</td>
<td>H</td>
<td>B—implant exchange, subpec to submam</td>
<td>2004—breast aug</td>
<td>B—Mentor MP 700 cc</td>
<td>Wise pattern</td>
<td>Submam</td>
</tr>
<tr>
<td>16</td>
<td>51</td>
<td>W</td>
<td>E—breast reconstruction after melanoma</td>
<td>2005—lumpectomy</td>
<td>B—Mentor MP 350 cc</td>
<td>Inframammary</td>
<td>Submam</td>
</tr>
<tr>
<td>17</td>
<td>48</td>
<td>W</td>
<td>D—sec rev bilateral complete capsulectomy</td>
<td>1991—primary aug</td>
<td>B—Mentor HP 600 cc</td>
<td>Periareolar</td>
<td>Submam</td>
</tr>
<tr>
<td>19</td>
<td>38</td>
<td>W</td>
<td>B—implant exchange, subpec to submam</td>
<td>2005—primary aug</td>
<td>B—Mentor HP 275 cc</td>
<td>Crescent mastopexy</td>
<td>Submam</td>
</tr>
</tbody>
</table>

Indications: A = primary aug; B = implant exchange; C = capsulotomy; D = capsulectomy with replacement; D2 = ruptured implant, capsulectomy with replacement; E = reconstructive surgery. Previous surgeries: RR = revision and replacement of breast implants. Size: Mentor MP = Mentor silicone implant moderate plus profile; Mentor HP = Mentor silicone implant high profile.
with implant replacement. One patient without CC had revision surgery for a size change and five patients were scheduling revision surgery for their contracture at the time this article was prepared. Nine patients were happy with their result and did not feel the need for any additional surgery.

Of the 21 breasts treated for existing CC, Baker scores ranged from greater than I (but less than II) to IV. Breasts with mild CC (Baker score of less than III) had significantly greater improvement with Singulair than breasts with severe CC (Baker score III and IV; \( P < .05 \)). All patients who had severe CC underwent revision surgery or were scheduling revision surgery. This was true even in patients who reported improvement of their CC. Statistically, the plane of implant placement did not significantly affect the response to Singulair.

### DISCUSSION

Our results in this preliminary study show that Singulair improves CC. However, because our study was retrospective and we did not have a well-matched population of negative controls, we cannot determine which patient variables predict a better response to Singulair. Unlike Accolate, the adverse event profile of Singulair is comparable to placebo, with the most common side effects being headache (18.4% vs 18.1%), influenza-like symptoms (4.2% vs 3.9%), abdominal pain (2.9% vs 2.5%), cough (2.7% vs 2.4%), and dyspepsia (2.1% vs 1.1%).¹⁶ Only one of our patients reported any side effect (fatigue). All other patients tolerated the treatment without any problems.

We were unable to make any correlation between duration of therapy and response to Singulair. Nine (47.4%) of the patients took Singulair for the full 90 days. Seven patients (36.8%) took Singulair for less than 90 days. In four of the patients who discontinued use, CC completely resolved and they stopped the medication because they felt they no longer needed it. Three patients stopped the medication early because they felt it was ineffective and scheduled surgery instead. Three patients (15.8%) took Singulair for more than 90 days. Two of these patients were being treated with Singulair prophylactically. One of them had a history of between eight and 10 revision procedures for CC dating back to 1988. Another had severe bilateral CC prior to surgery. Both of these patients began Singulair immediately after surgery and continued taking it for five and six months, respectively. Follow-up at 21 and 23 months after their surgery revealed that neither had redeveloped CC and both were pleased with their result. The third patient who took Singulair for more than 90 days continued it for six months because she felt the drug improved her CC and she elected to extend the duration of therapy.

We observed that breasts with mild CC (Baker score of less than III) had a greater likelihood of improvement than those with more severe contracture (Baker score III and IV). The exact molecular mechanism behind CC is not completely understood, although it is generally agreed that an inflammatory response causes periprosthetic scar formation. Leukotriene receptor antagonists are known to alter the inflammatory cascade and likely aid in the prevention of fibrosis associated with CC.⁷¹³ Perhaps Singulair is capable of ameliorating the lesser degrees of inflammation and fibrosis found in low-grade CC, but less likely to remodel the well-formed fibrotic capsule associated with
Baker score III or IV contracture. Three of the patients with severe contracture (Baker III or IV) felt that their contracture improved with Singulair, but all three proceeded to schedule or undergo revision surgery.

Future studies should include prospective, randomized double-blind studies with negative controls. Patients might be placed into one of four groups—primary augmentation ± mastopexy, implant exchange, revision surgery with capsulotomy, and revision surgery with capsulectomy. Only patients with silicone gel implants would be included to eliminate implant filler as a variable. Patients in each of these four groups should be randomized to receive 90 days of Singulair treatment. Each patient’s age, race, implant position, incision, time to contracture, and duration of treatment would be recorded. Degree of CC should be assessed using the Baker Scale at multiple intervals—one week, one month, six months, one year, and possibly three years—by at least two independent plastic surgeons blinded to whether or not the patients received treatment. A patient questionnaire could obtain follow-up data on patients who did not return for physician examination. Statistical analysis should be employed to determine whether Singulair significantly reduces the risk of developing CC and whether there are specific patient factors associated with treatment response. Because CC can develop after many years, long-term follow-up studies are warranted to determine the extended efficacy of Singulair.

CONCLUSIONS

Our article presents preliminary findings on the off-label use of Singulair for CC. The drug is well tolerated with minimal side effects; therefore, we recommend its application in patients with CC. There was a greater response in breasts with mild CC, so a course of Singulair should be started early. Because it prevented recurrence in two patients with previous severe contracture, we recommend prophylactic prescription in patients with a history of recurrent contracture. In patients who already have moderately advanced CC, Singulair is unlikely to reverse symptoms to the degree that revision can be avoided.

Disclosures

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