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The Effects of Zafirlukast on Capsular Contracture: Preliminary Report

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Abstract. Capsular contracture after breast augmentation is a distressing, troublesome event both for the patient and the surgeon. Fibrosis transforms the prosthesis into a hardened sphere, turning the initially satisfactory cosmetic result into a deformed mass. Treatment for capsular contracture can be either surgical, consisting of capsulotomy or capsulectomy with implant replacement, or pharmacologic, consisting of intracapsular instillation of steroids and antibiotics. The success rates for both types of treatment vary. Although capsular contracture is a multifactorial process, one common denominator in the successful treatment of this complication is believed to be the abatement of inflammation. Leukotriene antagonists have emerged recently as effective prophylactic agents for reactive airway diseases. Anecdotal reports have indicated that zafirlukast and montelukast effectively reverse capsular contracture. The authors investigated whether capsular contracture varies significantly over time after zafirlukast therapy by studying 20 women who had breast prostheses implanted and then experienced the development of capsular contracture. The results suggest that capsular contracture responds favorably to treatment with zafirlukast. The findings indicate that zafirlukast may reduce pain and breast capsule distortion for patients with long-standing contracture who either are not surgical candidates or do not wish to undergo surgery.

Key words: Capsular contracture—Mammary compliance—Zafirlukast

Capsular contracture is the most common problem and cause of patient dissatisfaction after augmentation mammaplasty with breast implants. The spectrum of postoperative results ranges from breasts that look and feel normal to those that exhibit varying degrees of unilateral asymmetry, distortion, firmness, and discomfort. The reported rates of this complication range from 0.5% to 30% [15,18].

Patients who undergo augmentation with an alloplastic implant all experience capsules around the prostheses. Breast firmness so marked as to result in a painful, hard breast, occasionally with visible distortion, has been termed fibrous capsular contracture [12,20]. A number of intraoperative and postoperative factors may be linked to capsular contracture. Unfortunately, because few strictly controlled studies have been conducted to investigate the causes and possible prevention of capsular contracture, there are as yet no definite data on the etiopathogenesis of this complication [7,19,45]. The incidence of capsular contracture varies depending on the type of implant used, the coating of the implant envelope, the position in which the implant is placed, and the intraoperative and postoperative precautions taken.

Textured implants are associated with a lower incidence of capsular contracture than smooth surfaced implants, whereas polyurethane foam-covered implants are reported to cause the lowest incidence of capsular contracture in long-term studies [14,15,47].

Numerous measures have been proposed and implemented to prevent capsular contracture both during surgery (e.g., meticulous hemostasis, suction catheters, a pocket, intraluminal instillation of steroids and antibiotics, textured implants, subpectoral implant placement, and perioperative antibiotics) and after surgery (e.g., breast massage, implant movement exercises, prolonged postoperative compression, and topical or oral vitamin E). Unfortunately, such treatments do not unfailingly prevent cases of capsular contracture [6,8,12,31,43].

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A number of treatments designed to reverse capsular contracture also have been proposed and used, all with varying success. These treatments may be either surgical (i.e., capsulotomy or capsulectomy, in which the implant is replaced or the plane of placement changed) or pharmacologic (e.g., delayed intracapsular instillation of steroids and antibiotics), although the success rate for these treatments also varies [10,11,32,36,37,51].

Although the process causing capsular contracture appears to be multifactorial, one common denominator in its successful treatment is believed to be the abatement of inflammation. The triggering of inflammation, and in some cases the development of capsular contracture, begins with the normal healing process. It is possible that the fluid retained around the breast implant after surgery causes ongoing inflammation. Pharmacologic inhibition of the inflammatory process has indeed become the main focus of current research [5,29,30,40].

Leukotriene antagonists have emerged recently as effective prophylactic agents in the management of reactive airway diseases [27,48]. Anecdotal reports and subsequent clinical trials have indicated that zafirlukast (Accolate; AstraZeneca Pharmaceuticals, Wilmington DE, USA) and montelukast (Singulair, Merk Sharp e Dohme Whitehouse Station NJ, USA) effectively reverse capsular contracture after breast augmentation, reportedly because they inhibit cysteinyl leukotrienes (LTC_4 LTD_4, and LTE_4) and their presumed suppressive effect on myofibroblasts, two factors presumed to cause contracture [23,41,44].

Since November 1996, zafirlukast has been prescribed millions of times. It is indicated for the preventive and long-term treatment of asthma in adults and children 12 years of age or older. It generally is well tolerated, although it does have possible side effects that include headache (12.9%), nausea (3.1%), and, extremely rarely, liver disease. A series of coincidences led to the discovery of the effects of zafirlukast on capsular contracture [13].

No studies in the literature have yet used an objective system to assess the effects of zafirlukast on capsular contracture. All the previous studies used a subjective measurement of capsular contracture. The most accurate means for objectively assessing the hardness of the breast after implant placement is the measurement of mammary compliance using the Anton Paar Mammacompliance system (Polytech Europe, Dieburg, Germany) [1–4,9,25,26]. The advantage of this system is that it does not include a descriptive part. The results are based exclusively on the measurements and objective data. Moreover, this system is easily reproducible during checkups, and provides an objective assessment of capsular contracture [2].

This study aimed to investigate whether capsular contracture varies significantly over time after zafirlukast treatment by studying a series of patients who had breast prostheses implanted and experienced the development of capsular contracture.

Materials and Methods

For the purposes of this study, we considered all the patients who came to our institution between September 2004 and June 2005 with mild or severe capsular contracture in at least one breast. We enrolled 20 women in whom 36 prostheses had been implanted. The reasons for the prosthesis implantation were augmentation mastoplasty for eight patients (total of 16 prosthesis), replacement after breast augmentation for four patients (8 prostheses), and mammary reconstruction for eight patients (12 prostheses). The mammary reconstruction was bilateral in one case (2 prostheses), monolateral with controlateral augmentation mammaplasty to achieve symmetry in three cases (6 prostheses), and monolateral in four cases (4 prostheses). A delayed reconstruction was performed in all cases.

We excluded from the study patients with liver, kidney, or lung disease, patients with chronic disease of the skin (psoriasis, sclerodermitis), patients who were pregnant, and patients older than 55 years. The age of the patients ranged from 25 to 54 years (mean, 36 years and 9 months; median, 32 years). The time elapsed since the prosthesis implantation ranged from 8 months to 3 years and 3 months (mean, 1 year and 6 months; median, 1 year and 1 month).

The implant was an anatomic implant filled with cohesive silicone gel in 17 cases, and a round double-lumen implant filled with silicone gel and saline solution in 10 cases. In the remaining 9 cases, the implant was a round implant filled with silicone gel. The size of the implants ranged from 165 to 440 g for the anatomic implants, from 200 to 400 g for the round double-lumen implants, and from 175 to 325 g for the round implants filled with silicone gel. All the double-lumen implants were filled with the recommended amount of saline solution, and all had a textured shell.

An inframammary approach and a retromammary pocket location were used in all the cases of augmentation mastoplasty. The same breast augmentation approach used in the first operation also was used in all the cases that involved prosthesis replacement (i.e., inframammary approach with a retromammary pocket location). The approach used for mastectomy with a retromuscular pocket location was used in the cases of mammary reconstruction.

All the patients were informed of the possible risks associated with the off-label use of zafirlukast. Once they had given their informed consent, they were enrolled in the study. All the patients enrolled underwent regular liver function tests. No changes in liver function were observed.

The patients received 20 mg of zafirlukast (Accolate) orally twice a day for 6 months. Because of this agent's well-documented adverse effects, including liver failure and hepatitis, the patients were offered hepatic profiles 0, 3, and 6 months after beginning the regimen, as well as the option to terminate the study at any time.

Breasts were assessed at the start of the study (T0), each month (T1, T2, T3, T4, and T5), and at the end of the study (T6) by means of the Anton Paar Mammacompliance system by one operator. Three independent evaluators also assessed the breasts at the same time points using the palpation method according to the Baker classification [2–4]. Capsular contracture scores thus obtained for each affected breast at each time point were compared with those from the other time points. The initial mammary compliance scores (baseline) were compared with those 3 and 6 months after therapy by means of the *t* test to verify their significance. The threshold level of significance was considered to be a *p* value less than 0.05.

Results

The mean values of mammary compliance obtained at the different time points were 55.89 at T0, 49.97 at T1, 47.74 at T2, 46.33 at T3, 45.19 at T4, 43.83 at T5, and 42.76 at T6 (Table 1, Fig. 1). When the capsular contracture of the breasts was grade I according to Baker's classification, the mean values of mammary compliance were 37.47 at T0 in 4 cases (11.1%), 37.56 at T1 in 5 cases (13.9%), 36.92 at T2 in 5 cases (13.9%), 36.2 at T3 in 5 cases (13.9%), 36.68 at T4 in 6 cases (16.6%), 37.02 at T5 in 8 cases (22.8%), and 36.92 at T6 in 10 cases (28.6%). When we observed grade II capsular contracture in the same group, the mean values of mammary compliance were 46.94 at T0 in 5 cases (13.9%), 43.71 at T1 in 8 cases (22.2%), 43.85 at T2 in 10 cases (27.8%), 44.18 at T3 in 15 cases (41.7%), 44.26 at T4 in 20 cases (55.6%), 44.28 at T5 in 21 cases (60%), and 43.45 at T6 in 19 cases (54.3%). For observed grade III capsular contracture, the mean values of mammary compliance were 56.63 at T0 in 19 cases (52.8%), 52.54 at T1 in 16 cases (44.5%), 51.66 at T2 in 17 cases (47.2%), 50.60 at T3 in 13 cases (36.1%), 51.94 at T4 in 10 cases (27.8%), 51.36 at T5 in 6 cases (17.2%), and 50.3 at T6 in 6 cases (17.1%). When capsular contracture was grade IV, the mean values of mammary compliance were 65.65 at T0 in 8 cases (22.2%), 58.7 at T1 in 7 cases (19.4%), 56.82 at T2 in 4 cases (11.1%), and 55.76 at T3 in 3 cases (8.3%), whereas there were no cases of grade IV capsular contracture at T4, T5, and T6 (Table 1).

The statistical analysis, performed with the *t* test, showed that there was a statistically significant difference in capsular contracture after treatment with zafirlukast between T0 and the subsequent measurements (T3 and T6) (*p* value 0.0000035 and 0.000000001).

We did not observe any major complications, except in one patient who experienced hypertension and decided to drop out of the study after 4 months. All the liver test results for the patients during the course of the study were normal.

Discussion

Capsular contracture is a common problem after placement of breast implants for augmentation or reconstruction. The precise mechanism by which the body produces this response to the implants is unknown. What we do know is that an inflammatory response that results in periprosthetic fibrosis occurs. The severity of this response appears to determine whether a patient exhibits distortion or a painful periprosthetic scar. Since early reports of severe capsular contracture in the literature, various means have been tried for correction or prevention of this disfiguring and potentially debilitating process [19].

Once capsular contracture develops, the current recommendations for treatment are breast massage, oral vitamin E therapy, and, finally, surgical intervention. However, not even surgery guarantees a successful outcome, as the 79% success rate of capsulectomy in recent series suggests. Open capsulotomy alone results a recurrence for up to 54% of patients. Moreover, secondary surgery carries a number of potential complications such as hematoma, infection, implant deflation and rupture, and breast asymmetry, as well as the need for further revision, which only adds to the cost for the patient [32,51].

Most surgeons agree that the best treatment for capsular contracture is prevention. Although it is difficult to predict the patients in whom severe contracture are likely to develop, a patient with a postoperative infection or hematoma is clearly at risk. In addition, patients with a history of hypertrophic scarring might be considered at risk for significant contracture after breast augmentation. These "high-risk" groups of women may benefit from prophylactic treatment aimed at reducing the inflammatory response [8,31,43].

Although we do not completely understand the cause of capsular contracture after breast augmentation or reconstruction, an exaggerated inflammatory response does occur. The role of specific cells such as the macrophage or mast cell, although yet to be fully elucidated, is supported by previous studies. It may be possible to modify the leukotriene receptor antagonists (LTRAs) so as to alter the inflammatory cascade, thereby preventing the severe fibrotic reaction associated with capsular contracture [23].

The role of the macrophage and the mast cell may be particularly important in the physiologic mechanisms by which LTRAs inhibit capsular contracture. It has been suggested that myofibroblasts are the cause of excess collagen production and extracellular matrix deposition because they share the properties of both fibroblasts and smooth muscle cells [29,35,39,40,46,49]. In addition, Baker et al. [5] in 1981 specifically indicated the myofibroblast as the probable cause of capsular contracture, postulating that drugs inhibiting myofibroblast smooth muscle activity would help to prevent capsular contracture.

Table 1. Data from the study group

			T0 (Baseline)		T1 (1 month)		T2 (2 months)		T3 (3 months)		T4 (4 months)		T5 (5 months)		T6 (6 months)	
Patient	Breast	Group	Compl.	Baker	Compl.	Baker	Compl.	Baker	Compl.	Baker	Compl.	Baker	Compl.	Baker	Compl.	Baker
1	Left	AM	50.7	III	45.7	II	43.1	II	42.5	II	42.0	II	40.1	II	36.5	I
	Right	AM	50.4	III	46.7	II	42.5	II	42.3	II	41.6	II	39.9	II	38.0	I
2	Left	AM	52.2	III	45.6	II	43.8	II	42.6	II	41.8	II	41.0	II	40.4	II
	Right	AM	57.7	III	52.3	III	49.7	III	47.2	III	45.8	II	44.9	II	44.2	II
3	Left	AM	59.3	III	54.6	III	49.8	III	45.7	II	44.2	II	41.4	II	40.1	II
	Right	AM	35.2	I	34.8	I	34.5	1	34.2	I	34.1	I	34.0	I	33.6	I
4	Left	AM	68.3	IV	61.8	IV	57.4	III	54.6	III	52.8	III	51.1	III	49.8	III
	Right	AM	59.5	III	53.6	III	50.5	III	48.2	III	46.6	II	44.3	II	43.1	II
5	Left	AM	63.4	IV	56.8	IV	53.9	III	52.1	III	51.5	II	49.9	III	48.9	III
	Right	AM	48.5	II	45.3	II	43.7	II	41.2	II	40.3	I	39.7	I	38.9	I
6	Left	AM	53.7	III	48.6	III	45.9	II	43.7	II	42.8	II	41.6	II	40.8	II
	Right	AM	54.9	III	49.2	III	47.8	II	46.5	II	42.9	II	42.1	II	41.5	II
7	Left	AM	66.8	IV	58.8	III	56.3	III	54.7	III	52.1	III	50.5	II	48.9	II
	Right	AM	57.6	III	51.4	III	49.3	III	47.7	II	46.2	II	45.1	II	439	II
8	Left	AM	48.4	II	44.3	II	43.2	II	41.5	II	40.8	II	39.5	I	38.0	I
	Right	AM	56.6	III	51.2	III	48.8	III	46.3	II	44.5	II	42.8	II	40.9	II
9	Left	RA	67.9	IV	60.2	IV	57.5	IV	55.9	IV	54.1	III	52.3	III	50.9	III
	Right	RA	58.4	III	52.3	III	50.6	III	48.9	III	47.6	II	45.9	II	44.3	II
10	Left	RA	58.3	III	52.9	III	51.3	III	50.5	III	48.9	III	47.1	II	44.8	II
	Right	RA	40.2	I	39.3	I	38.7	I	38.3	I	37.8	I	37.6	I	37.8	I
11	Left	RA	44.7	II	41.5	I	39.9	I	38.7	I	38.2	I	38.0	I	37.8	I
	Right	RA	59.2	III	53.4	III	50.8	III	48.7	II	47.7	II	46.4	II	45.2	II
12	Left	RA	46.5	II	42.4	II	41.8	II	41.0	II	40.2	II	40.0	I	39.5	I
	Right	RA	59.6	III	53.5	III	51.1	III	49.8	III	48.1	II	47.2	II	45.8	II
13	Left	MR	58.9	III	52.4	III	50.6	III	48.7	III	47.1	II	46.0	II	44.9	II
	Right	MR	60.2	III	53.7	III	51.5	III	49.8	III	48.3	II	47.1	II	45.4	II
14	Left	AM	35.1	I	33.9	I	33.6	I	32.8	I	32.6	I	32.3	II	32.3	I
	Right	MR	63.3	IV	55.6	IV	53.1	III	51.6	III	50.7	III	50.0	III	48.9	III
15	Left	AM	46.6	II	43.1	II	42.5	II	41.9	II	41.2	II	40.4	II	40.2	II
	Right	MR	53.9	III	46.6	II	44.2	II	43.9	II	43.0	II	42.7	II	42.3	II
16	Left	MR	55.2	III	50.0	III	48.7	III	46.9	II	45.1	II	43.8	II	43.1	II
	Right	AM	39.4	I	38.3	I	37.9	I	37.3	I	37.1	I	37.0	I	36.8	I
17	Right	MR	61.0	IV	57.9	IV	55.4	IV	52.1	III	51.7	III	50.9	III	50.1	III
18	Right	MR	69.3	IV	60.3	IV	57.3	IV	55.6	IV	53.9	III	/	/	/	/
19	Left	MR	59.8	III	52.8	III	50.9	III	49.7	III	48.8	III	47.6	II	45.9	II
20	Right	MR	64.4	IV	58.3	IV	57.1	IV	55.8	IV	54.9	III	54.0	III	53.2	III
	Mean		55.89		49.97		47.74		46.33		45.19		43.83		42.76	

Compl, Compliance; AM, augmentation mammaplasty; RA, replacement after augmentation; MR, mammary reconstruction

A report by Niessen and Spauwen [34] suggests that the macrophage is a pivotal intermediary between the inflammatory phase and scar formation. The macrophage release of fibroblast-activating cytokines, which transforms growth factor-β, platelet-derived growth factor and interleukins, is important in collagen production and organization as well as extracellular matrix degradation. Niessen and Spauwen [34] suggest that all cellular and immunologic processes, and not fibroblast activity alone, lead to the formation of excessive scar tissue. There also may be a relationship between mast cells and scars, as suggested by the fact that mast cells are found in dermal collagen bundles, as well as in higher numbers in hypertrophic scars than in "normal" scars. The mast cell response, characterized by histamine-like activity and capable of stimulating collagen formation, is markedly increased in keloid tissue. The result is an increase in the collagen matrix found in scar tissue. This response is directly inhibited by LTRAs, which seem capable of reducing the rate of capsular contracture [34,44].

Our results in this preliminary study show a favorable response of capsular contracture to zafirlukast treatment in a group of patients who underwent subglandular augmentation mastoplasty, subglandular replacement after breast augmentation, and submuscular mammary reconstruction with cohesive silicone gel–filled, silicone gel–filled or silicone gel and saline solution–filled, textured wall implants and took zafirlukast for at least 3 months. All the treated breasts responded either completely or

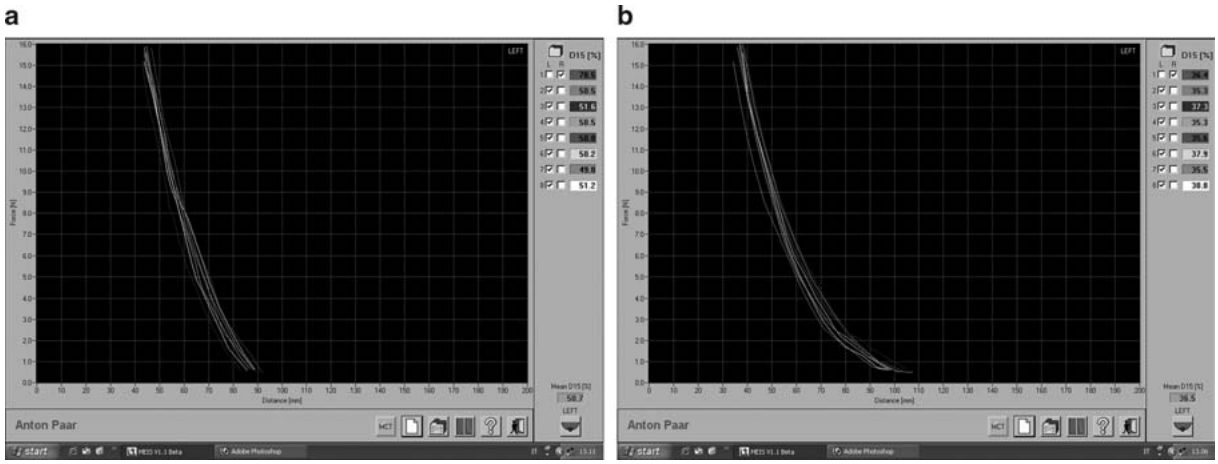

Fig. 1. Mammary compliance graphs for the same patient before (**a**) and after 6 months of zafirlukast therapy (**b**).

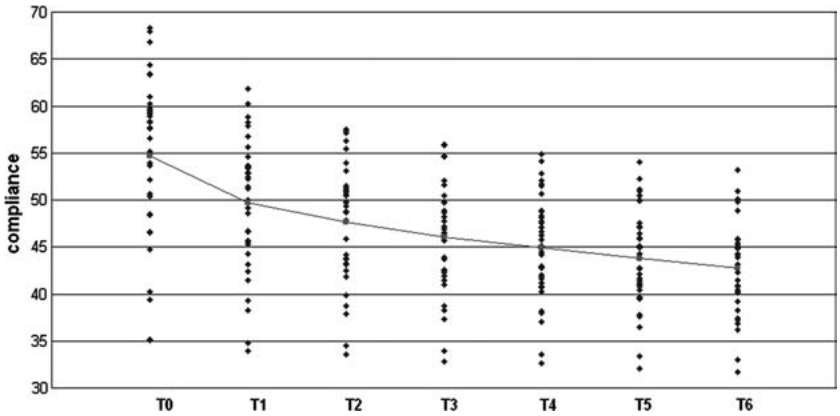

Fig. 2. Changes over time in mammary compliance values for the patients who received zafirlukast.

partially to the leukotriene antagonist at 3 and 6 months (all results statistically significant). We observed a reduced mammary compliance in these patients of 10.59% after 1 month, 17.10% after 3 months, and 23.49% after 6 months. Moreover, in the same group we observed a 1-point decrease in capsular contracture (according to Baker's classification) in 27 cases, and a 2-point decrease in 3 cases.

In the evaluation of mammary compliance, great importance is attributed to graphs because they show the severity of capsular contracture. Curvilinear graphs indicate mild capsular contracture, whereas rectilinear graphs indicate severe capsular contracture. In our study, the graphs show a remarkable improvement in the breasts after zafirlukast treatment (Fig. 2a and b).

It is noteworthy that the higher the mammary compliance value, the greater the reduction in capsular contracture after 1 month of zafirlukast therapy. Another noteworthy point is that the reduction in the mammary compliance value is positively correlated with the time elapsed since the development of capsular contracture: the shorter the time, the greater the reduction. Moreover, in women whose anatomic implant was filled with cohesive silicone gel, the presence of capsular contracture resulted, over time, in the implant becoming distorted because of constriction. Although we observed improved mammary compliance in such cases, the aesthetic result was unsatisfactory due to the deformity of the implant, which in turn meant the prosthesis had to be replaced. We also observed a decrease in the mammary compliance values for the breast that did not present with capsular contracture, although this reduction was less marked than that observed for the breast with capsular contracture.

Some studies have reported that other leukotriene antagonists, such as montelukast at a oral dose of 10 mg daily, also may reverse capsular contracture after breast augmentation. Leukotriene modifiers, commonly used for persistent asthma, usually are well tolerated.

The use of zafirlukast warrants careful monitoring because normal doses of zafirlukast have been reported to cause liver failure in a very small number of patients, most of whom were women presenting with anorexia, right upper quadrant pain, pruritus, and jaundice. The onset of hepatocellular dysfunction

occurred 2 to 18 months after the start of zafirlukast therapy [24,50].

Data provided by the Adverse Event Reporting System from the Office of Postmarketing Drug Risk Assessment, a branch of the Department of Health and Human Services' Center for Drug Evaluation and Research, showed 66 cases of hepatitis or liver failure among patients receiving a normal dose of zafirlukast. A total of 23 deaths were recorded, 12 after liver failure, and all involving patients receiving a normal dose of zafirlukast. Two patients required liver transplants. No prior liver disease had been noted among the patients, and 13 were taking no other medications.

Controlled clinical trials of zafirlukast have reported elevations of one or more liver function test results [16]. Premarketing studies have shown asymptomatic elevations of liver function test results (2 to 3 times above normal) in 1.5% of 4,058 patients receiving zafirlukast, and in 1.1% of 2,032 patients receiving placebo (not statistically significant) [38].

Clinical trials of montelukast have not shown any significant difference in liver function abnormalities between the montelukast group and the placebo group. The findings showed an increased alanine aminotransferase level for 2.1% of 1,955 montelukast recipients, as compared with 2% of 1,180 placebo recipients, and self-limited, transient increases in aspartate aminotransferase levels for 1.6% of montelukast recipients, as compared with 1.2% of placebo recipients [39]. There have, however, been reports of drug-induced hepatitis from montelukast [22].

A review of all the reported leukotriene modifier-induced hepatitis cases showed that hepatic toxicity may develop within weeks or as late as 13 months after the start of therapy. The increasing use of these drugs, coupled with the monitoring of liver function, may lead to the emergence of more asymptomatic cases. On the basis of a literature review, we recommend that liver function be tested within 4 weeks after the start of therapy using any leukotriene modifier, and that testing be repeated at 3, 6, and 12 months [42]

Some studies also have reported that leukotriene antagonists, such as zafirlukast and montelukast, may cause systemic eosinophilia and small-vessel vasculitis (i.e., Churg-Strauss syndrome) [21]. One possible explanation for these reports is the unmasking of previously unsuspected cases of Churg–strauss syndrome through the reduction of oral steroid therapy and its replacement with LTRA [28]. Given the possibility that leukotriene antagonists may directly activate Churg-Strauss syndrome, LTRA treatment should be withdrawn for any patient who experiences systemic symptoms with hypereosinophilia [33].

Leukotriene antagonists have, despite the aforementioned complications, been widely used for the treatment of asthma since 1996, and currently are still on the market. After 10 years of experience, we are fully aware of both the advantages and drawbacks of this family of drugs.

Conclusions

In our preliminary study, we found that zafirlukast is highly effective in the treatment of established capsular contracture, although the precise mechanism by which the leukotriene receptor antagonists reduce or prevent capsular contracture is not yet fully understood. Longer follow-up studies are warranted to determine the long-term efficacy of zafirlukast and other leukotriene antagonists, such as montelukast, in the prevention and treatment of capsular contracture. Finally, further studies should be designed to investigate how long the effects of leukotriene antagonists last after therapy is discontinued. For these reasons, we have scheduled a double-blind study for a better understanding of the precise mechanisms underlying the effectiveness of zafirlukast and other leukotriene antagonists in the treatment of capsular contracture.

Zafirlukast should not be prescribed for patients with hepatic dysfunction. Moreover, serum transaminase levels should be monitored periodically and the drug suspended if hepatotoxic effects emerge. Mild hepatic dysfunction seems to reverse after discontinuation of the drug in most cases, although this condition has been known to progress to liver failure.

Finally, and importantly, the use of zafirlukast and other leukotriene antagonists for the treatment of capsular contracture is an off-label procedure and, as such, warrants an understanding of the legal requirements and ramifications. In addition, we recommend that specific informed consent be obtained for off-label use of this drug. Although this requires some additional work and effort for both the surgeon and patient, it does provide the patient with more thorough information and, at the same time, offers the surgeon greater protection against the legal misinterpretation and maneuvering that might result. We recommend that the informed consent process include discussions on the medical reasons for approving the off-label use of zafirlukast and the potential benefits to the patient [17].

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