Ursodeoxycholic Acid as a Chemopreventive Agent in Patients With Ulcerative Colitis and Primary Sclerosing Cholangitis

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See editorial on page 1139.

Background & Aims: Ursodeoxycholic acid (UDCA) has shown effectiveness as a colon cancer chemopreventive agent in preclinical studies. In addition, a recent report suggests that it also may decrease the risk for developing colorectal dysplasia in patients with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC). We sought to evaluate the effect of UDCA on colorectal neoplasia in a group of patients with UC and PSC enrolled in a randomized, placebo-controlled trial.

Methods: From a prior, randomized, placebo-controlled trial of UDCA therapy in PSC at our center, we followed-up patients with concomitant UC to assess the effect of UDCA on the development of colorectal dysplasia and cancer as compared with placebo.

Results: Fifty-two subjects were followed-up for a total of 355 person-years. Those originally assigned to receive UDCA had a relative risk of 0.26 for developing colorectal dysplasia or cancer (95% confidence interval, 0.06–0.92; P = 0.034). Many of the patients originally assigned to the placebo group eventually received open-label UDCA. Assigning these patients to the UDCA group from the time they began active therapy did not change the magnitude of the protective effect (relative risk, 0.26; 95% confidence interval, 0.07–0.99; P = 0.049). Conclusions: UDCA significantly decreases the risk for developing colorectal dysplasia or cancer in patients with UC and PSC.

Ulcerative colitis (UC) is associated with an increased risk for developing colorectal cancer and precancerous dysplastic epithelial changes.1 UC also is associated with primary sclerosing cholangitis (PSC), a chronic cholestatic liver disease characterized by inflammation and scarring of the bile ducts.2 Patients with both UC and PSC may be at higher risk for developing colorectal aneuploidy, dysplasia, or cancer than UC patients without PSC, although some studies have not shown a further increase in risk.12–14

Ursodeoxycholic acid (UDCA), a synthetic bile acid, has been shown to have colon cancer chemopreventive effects in preclinical studies.15–20 In addition, a recent report has suggested that UDCA also decreases the risk for developing dysplasia in UC patients with PSC.21 We have previously conducted a randomized, placebo-controlled study using UDCA in patients with PSC in an attempt to influence liver disease progression.22 Among 105 patients in that study, 85 had concomitant UC. This cohort was studied to compare the cumulative incidence of colorectal dysplasia and cancer in those treated with UDCA compared with placebo.

Materials and Methods

The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board. All patients with UC from the initial PSC-UDCA trial potentially were eligible for the current study. The diagnosis of PSC was based on typical cholangiographic and liver biopsy criteria,22 and the diagnosis of UC was based on typical clinical, endoscopic, and histologic criteria. Patients with dysplasia, colon cancer, or colectomy before or within 6 months of entering the initial study were excluded. In addition, patients without at least one surveillance colonoscopy with biopsy examination after entering the UDCA trial and those denying research authorization for review of their medical records were excluded. The database from the previous UDCA trial and the medical records of these subjects were reviewed to obtain data on demographics and clinical features. Colonoscopic surveillance biopsy results (and colectomy if performed) were reviewed to identify the development of dysplasia or cancer. Follow-up was censored at the time of first dysplasia detection, last colonoscopy, colectomy,

Abbreviations used in this paper: DCA, deoxycholic acid; PSC, primary sclerosing cholangitis.
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or death. Dysplasia occurring in a lesion with the typical appearance of an adenoma was not included in this analysis if biopsy samples from the surrounding mucosa showed no dysplasia.\textsuperscript{23,24} Cases of dysplasia diagnosed elsewhere were included only if review by an experienced gastrointestinal pathologist at our institution, unaware of this study and thus blinded to treatment group, confirmed the presence of dysplasia. Any diagnosis of dysplasia required confirmation by a second experienced gastrointestinal pathologist.

The primary end point was the development of colorectal dysplasia or cancer. The primary analysis was performed using Poisson regression in an intention-to-treat analysis, with patients analyzed according to the group to which they were assigned initially (UDCA vs. placebo). After the placebo-controlled study of UDCA for treatment of liver disease,\textsuperscript{22} some of the placebo-treated patients were switched to open-label UDCA. The analysis was thus repeated using UDCA as a time-dependent covariate in the regression model. In this preplanned secondary analysis, the effect of UDCA was modeled as applicable for all times after first administration of UDCA. Other covariates (nonsteroidal anti-inflammatory drugs, sulfasalazine, or folic acid use, PSC and UC duration, and age at diagnosis of UC) were analyzed by sequential inclusion of one covariate and UDCA in a Cox regression model. The study was powered to detect a 60% reduction in the primary end point (i.e., 20% in the placebo group vs. 8% in the UDCA group) using a 2-sided test for proportions with \( \alpha = 0.05, \beta = 0.8 \) and 85 subjects.

**Results**

Of the 85 patients with UC from the original study, 33 (39%) were excluded, leaving 52 patients in this follow-up study. Twenty-four patients were excluded because they were inappropriate for the present study: 17 (20%) had proctocolectomy before study entry, 5 (6%) had cancer or dysplasia diagnosed before or within 6 months of study entry, 1 diagnosis was changed to Crohn’s disease, and 1 died shortly after entering the original study. Thus, only 9 patients (10% of the original cohort) who would have been appropriate for this follow-up study were excluded (1 refused to participate and 8 were lost to follow-up). The median age at study entry was 43 years (range, 21–68) and 29 (56%) were men. Twenty-three (44%) were treated initially with placebo and 29 (56%) with UDCA. During the study, patients were treated with UDCA for a median of 42 months (range, 15–75 month) and with placebo for 40 months (range, 12–72 month). The 2 groups had similar clinical features, as outlined in Table 1. The median duration of UC at the time of last colonoscopy was 15 years (range, 1–36 years). The extent of colitis was known in 46 patients, with all having pancolitis. All patients were Child-Pugh class A at study entry. There were 189 person-years of follow-up in the UDCA group and 166 in the placebo group. The intensity of colonoscopic surveillance was similar in the 2 groups in terms of the number of colonoscopies (median, 3; range, 1–9 in both groups; mean, 3.96 UDCA vs. 3.65 placebo), the average number of biopsies per colonoscopy (22 UDCA vs. 20 placebo), and the median time between surveillance colonoscopies (25.5 months UDCA vs. 23.6 months placebo).

Two patients had sporadic adenomas as defined earlier that were not counted as dysplasia. Four had dysplasia diagnosed elsewhere. When reviewed at our institution by a pathologist blinded to this study, 3 were confirmed as having dysplasia and 1 was not. Three patients were considered indefinite for dysplasia. One of these later developed a cancer, which is counted in the initial analysis. The other 2 (1 in each group) were counted as no dysplasia initially.

Colorectal neoplasia developed in 3 patients (10%) initially assigned to the UDCA group (all dysplasia) and in 8 patients (35%) initially assigned to the placebo group (2 cancer, 6 dysplasia). In an intention-to-treat analysis, using a Poisson regression model, the relative risk for dysplasia or cancer in the patients initially assigned to the UDCA group compared with placebo was 0.26 (95% confidence interval, 0.06–0.92; \( P = 0.034 \)). Figure 1 shows the survival free of dysplasia or cancer in each group over time.

Sixteen patients (70%) initially assigned to placebo were treated eventually with open-label UDCA for an average of 57 months (range, 5–77 months). Assigning these patients to the UDCA group from the time they began UDCA did not change the magnitude of the risk reduction (relative risk, 0.26; 95% confidence interval, 0.07–0.99; \( P = 0.049 \)).

There was no significant association between the use of nonsteroidal anti-inflammatory drugs, folic acid, or aminosaliclylates and the development of dysplasia or cancer in univariate analyses or in Cox proportional hazards regression when included as a covariate with treatment group. Similarly, inclusion of age at diagnosis

| Table 1. Clinical Features of the Study Patients According to Initial Randomized Treatment Group |
|-------------------------------------------|-----------------|-----------|
| Age at study entry, yr                    | UDCA            | Placebo   | \( P \) value |
| Age at UC diagnosis, yr                   | 40 (22–65)      | 46 (21–68)| 0.13        |
| Age at PSC diagnosis, yr                  | 29 (7–65)       | 35 (18–62)| 0.05        |
| Age at study entry, yr                    | 38 (20–64)      | 44 (21–65)| 0.15        |
| Duration of UC, yr                        | 13 (2–36)       | 12 (1–33) | 0.97        |
| Duration of PSC, yr                       | 9 (3–15)        | 9 (1–17)  | 0.95        |
| Sex, % men                                | 59              | 52        | 0.64        |

NOTE. Except for sex, values represent medians and ranges, and \( P \) values are based on 2-sample \( t \) test. For sex, the \( P \) value is based on the \( \chi^2 \) test. Duration of UC, as of last colonoscopy, duration of PSC, at study end.
of UC and duration of PSC or UC in the regression model did not significantly change the results. Because all patients had pancolitis, we were unable to analyze the effect of colitis extent on the risk for developing dysplasia or cancer. All variables considered in the regression analysis and the corresponding P values are listed in Table 2. There were 8 deaths during follow-up, 4 (14%) in the UDCA group and 4 (17%) in the placebo group (P = 1.0).

When the 2 patients with indefinite dysplasia were included in the dysplasia group, the results of the primary or secondary analyses did not change significantly.

The 2 patients who developed colon cancer were assigned initially to the placebo group, but the cancers developed while they were taking open-label UDCA. One of these patients had developed low-grade dysplasia while on placebo and was diagnosed with cancer 4 years after starting open-label UDCA. The second was diagnosed with cancer 22 months after starting open-label UDCA.

Discussion

Our comparison of colorectal neoplasia development in PSC-UC patients entered into a randomized, placebo-controlled trial suggests a significant chemoprotective effect for UDCA in these patients, with a 74% reduction in the risk for dysplasia or cancer in those assigned to the UDCA group.

The rationale for using UDCA as a chemopreventive agent is based on in vitro and animal models and uncontrolled clinical studies. UDCA inhibits proliferation of colon cancer cell lines in vitro, and in rats it significantly decreased the size and number of colon tumors induced by N-methyl-N-nitrosourea or azoxymethane. In some studies, UDCA was better than piroxicam, a known chemopreventive agent.

Higher fecal and serum deoxycholic acid (DCA) concentrations have been shown in patients with UC and colorectal dysplasia or cancer and in noncolitis patients with adenomas and cancers, implicating DCA as a possible carcinogen. In some studies, UDCA decreases fecal levels of DCA, suggesting that alteration of the colonic bile acid milieu might be a mechanism for the chemoprotective effects of UDCA. Other potential mechanisms, perhaps occurring through alteration of bile acids, include disruption of changes in protein kinase C isoforms induced by carcinogens, modulation of colonic mucosal arachidonic acid metabolism, suppression of telomerase activity and the development of aberrant crypt foci, enhanced tumor surveillance and eradication by increasing expression of colonic major histocompatibility complex antigens, or inhibition of cyclooxygenase-2 expression.

It also has been reported that UDCA decreases the risk for dysplasia in PSC-UC patients. In this retrospective case-control study of 59 subjects with PSC and UC, 26 had dysplasia and 33 did not. The use of UDCA was associated with a significant reduction in the odds of developing dysplasia (adjusted odds ratio, 0.14; 95% confidence interval, 0.03–0.64). However, despite this degree of apparent protection, 50% of the subjects treated with UDCA developed dysplasia. Furthermore, the control group had an unusually high rate of dysplasia.

Table 2. Covariates Considered in the Prediction of Dysplasia or Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dysplasia or cancer</th>
<th>Univariate P value</th>
<th>Cox PH P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsteroidal anti-inflammatory drug use</td>
<td>14% (5/35)</td>
<td>0% (0/10)</td>
<td>0.57</td>
</tr>
<tr>
<td>Folic acid use</td>
<td>67% (26/39)</td>
<td>55% (6/11)</td>
<td>0.50</td>
</tr>
<tr>
<td>Aminosalicylate use</td>
<td>85% (34/40)</td>
<td>100% (11/11)</td>
<td>0.32</td>
</tr>
<tr>
<td>Age at UC diagnosis</td>
<td>33.0 (17, 54)</td>
<td>33.5 (18, 62)</td>
<td>0.91</td>
</tr>
<tr>
<td>UC duration</td>
<td>8.7 (0.01, 33.7)</td>
<td>10.3 (0.6, 27.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>PSC duration</td>
<td>1.4 (0, 6.9)</td>
<td>2.0 (0, 13.3)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

NOTE. Age and duration data represent medians and ranges, whereas binomial data represent % and counts. For the univariate analysis, P values are based on Fisher exact test for binomial data and 2-sample t test for continuous data. The Cox proportional hazards (PH) P values are for the respective covariate when included in a model together with randomized treatment group.
(72%), and the UDCA-treated patients were older at diagnosis of colitis and had a shorter duration of colitis, raising questions about bias in this study. Even if we include the indefinite dysplasia cases in our study, the rates of dysplasia do not come close to the rates reported in this study.

In another study published in abstract form, the protective effect of UDCA was less impressive. In this analysis of 120 patients with UC and PSC, proportional hazards modeling indicated a nonsignificant 35% reduction in cancer or dysplasia in those treated with UDCA compared with patients not treated with UDCA.

Our placebo-controlled study showed a 74% reduction in the risk for development of colorectal neoplasia in patients with UC and PSC who were treated with UDCA. These results must be interpreted with some caution, however, because the 2 cancers seen were in patients initially assigned to placebo, but who subsequently were taking open-label UDCA. Nonetheless, our results, together with the results of a previous report on the chemoprotective effect of UDCA in these patients, warrants further research into the mechanisms involved in the chemoprotective effects of UDCA and into identifying which patients are likely to benefit from this therapy. Furthermore, a study of the chemoprotective effects of UDCA in the larger population with UC but not PSC is needed.

References


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