Protease inhibitors for preventing complications associated with ERCP: an updated meta-analysis

Takeshi Seta, MD, Yoshinori Noguchi, MD, MPH

Wakayma, Aichi, Japan

Background and Objectives: The prophylactic use of protease inhibitors in patients undergoing ERCP is still controversial. Our purpose was to evaluate the efficacy of protease inhibitors in preventing ERCP-associated complications.

Design and Setting: Meta-analysis; randomized trials that evaluated the efficacy of protease inhibitors were identified.

Patients: A total of 4966 patients were evaluated.

Main Outcome Measurements: ERCP-associated pancreatitis, hyperamylasemia, abdominal pain, and death.

Results: Eighteen studies (19 cohorts) met the inclusion criteria. Overall results for protease inhibitors showed a significant but small risk reduction in ERCP-associated pancreatitis (pooled risk difference [RD]: −0.029; 95% CI, −0.051 to −0.008 and the number needed to treat, 34.5; 95% CI, 19.6-125). Subgroup analysis in 8 high-quality studies showed a borderline significant efficacy (pooled RD, −0.027; 95% CI, −0.051 to −0.004). Subgroup analysis in 8 gabexate studies did not show significant efficacy (pooled RD, −0.030; 95% CI, −0.062 to 0.003). Subgroup analysis in 5 ulinastatin studies was significant (pooled RD, −0.035; 95% CI, −0.063 to −0.006). Two high-quality studies on ulinastatin yielded nonsignificant results. Analyses for the other outcomes were all nonsignificant. Sensitivity analysis showed that the effect size and level of statistical significance were decreased with increasing study quality.

Conclusions: At present, there is no solid evidence to support the use of protease inhibitors to prevent ERCP-associated complications. Although overall and ulinastatin subgroup analyses showed a small risk reduction for pancreatitis, it seems very possible that low-quality primary studies produced a veneer of efficacy. (Gastrointest Endosc 2011;73:700-6.)

Protease inhibitors, including gabexate mesylate and aprotinin, are used to prevent complications associated with ERCP. Several studies have examined the efficacy of protease inhibitors in preventing complications associated with ERCP. One such study showed that protease inhibitors were ineffective for preventing pancreatitis, hyperamylasemia, or abdominal pain associated with ERCP.[1] The other showed that the protease inhibitor gabexate mesylate was effective in preventing pancreatitis and abdominal pain after ERCP.[2] One randomized, controlled trial (RCT) showed that ulinastatin prevents complications associated with ERCP,[3] and the other was not effective in preventing complications.[4] Three meta-analyses did not significantly show the efficacy of gabexate mesylate in preventing pancreatitis, hyperamylasemia, and abdominal pain associated with ERCP.[5-7] A recent meta-analysis by Chen et al[8] showed that ulinastatin had a significant efficacy in preventing post-ERCP pancreatitis. Thus, the results of previous studies concerning the efficacy of protease inhibitors for post-ERCP pancreatitis are inconsistent.

Abbreviations: CI, confidence interval; D-L, DerSimonian-Laird; M-H, Mantel-Haenszel; NNT, number needed to treat; RCT, randomized, controlled trial; RD, risk difference.

DISCLOSURE: *The authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2010.09.022

Received June 29, 2010. Accepted September 8, 2010.

Current affiliations: Division of Gastroenterology and Hepatology (T.S.), Japanese Red Cross Society Wakayama Medical Center, Wakayama, Japan, Division of General Internal Medicine (Y.N.), Japanese Red Cross Society Nagoya Daini Red Cross Hospital, Aichi, Japan.

Reprint requests: Yoshinori Noguchi, MD, MPH, Division of General Internal Medicine, Japanese Red Cross Society Nagoya Daini Red Cross Hospital, Myoken-cho 2-9, Showa-ku, Nagoya-city 466-8650 Aichi, Japan.

If you would like to chat with an author of this article, you may contact Dr Noguchi at yoshi-noguchi@umin.ac.jp.

Therefore, we attempted to perform a new meta-analysis evaluating protease inhibitors including aprotinin, gabexate, and ulinastatin for preventing complications associated with ERCP.

METHODS

Literature search

Reports of RCTs examining the efficacy of protease inhibitors in preventing complications associated with ERCP were identified by systematically searching Medline, the Cochrane Library, Journal@ovid databases, and Japana Centra Revuo Medicina for publications from January 1966 to June 2010. References of review articles or previously published meta-analyses were also searched manually. Key terms used for searching were "pancreatitis," "protease inhibitors," "endoscopic retrograde cholangiopancreatography," "ERCP," and "complications."

Inclusion and exclusion criteria

A report was included in the analysis if the study was (1) an RCT of protease inhibitors and (2) written in English or Japanese or if it had an abstract in 1 of these languages. The bibliographies of original articles and meta-analyses were also inspected for further appropriate articles not initially identified. All authors decided independently which reports should be included for analysis. Any disagreements were settled by consensus decision.

Furthermore, for final inclusion, a study had to (1) include a treatment intervention (protease inhibitors) and concurrent control group (by using placebo, not another kind of protease inhibitors) to prevent complications associated with ERCP; (2) allocate study subjects randomly to the intervention and control groups; (3) administer protease inhibitors by intravenous infusion; and (4) report relevant outcomes. No limitations were placed on age or sex of patients or cause of ERCP-related complications.

Outcome measures

The following outcomes were used to measure the effectiveness of protease inhibitors for preventing complications associated with ERCP: (1) pancreatitis, (2) hyperamylasemia, (3) abdominal pain, and (4) death. The definitions of pancreatitis and hyperamylasemia are described in the Results section.

Quality assessment for primary studies

The quality of primary studies was assessed as described by Jadad et al.[9] This method assesses whether the study is randomized, the appropriateness of randomization if present, whether the study is double-blind, the appropriateness of double-blinding if present, and withdrawals/dropouts, by using a score of 0 or 1 for each item. Total score thus ranges from 0 to 5. We defined studies with a Jadad score of 3 points and more as high-quality in this meta-analysis.

Take-home Message

- Although overall and ulinastatin subgroup analyses showed a small risk reduction in pancreatitis, it seems very possible that low-quality primary studies produced a veneer of efficacy.

Data extraction

All authors independently read all identified articles and extracted analyzable data. Areas of disagreement or uncertainty were adjudicated among all researchers.

Statistical analysis

We calculated a risk difference (RD) for the primary outcome of the trials and weighted pooled estimates for binary data. A fixed-effects model weighted by the Mantel-Haenszel (M-H) method was used for pooling the RD,[10] followed by a test of homogeneity. Homogeneity among studies was assessed by using the I^2 test.[11] If the I^2 was 25% or more, the hypothesis of homogeneity was rejected and a random-effects model of the DerSimonian-Laird (D-L) method was used.[12] Otherwise, fixed-effects model of the Mantel-Haenszel (M-H) method was used. The potential for publication bias was examined by the funnel plot method,[13] and the statistical significance of differences was evaluated in accordance with the methods of Begg and Mazumdar[14] or Egger et al.[15] Given the observed RD, the number needed to treat (NNT) to prevent 1 adverse effect was also used as a measure of treatment effect. For computation, NNT = 1/RD. All statistical analyses were performed with the aid of STATA statistical software (Stata/SE 11 for Windows 2009; StataCorp, College Station, Tex). Results are expressed as means and 95% confidence intervals (CIs), unless indicated otherwise. A P value $<.05$ was considered statistically significant.

RESULTS

Selection and features of studies

The database search yielded 24 articles,[1-4,16-35] and a manual search of bibliographies in these articles added 1 German article[36] and 3 Chinese articles.[37-39] Of the 28 articles, 18 met the inclusion criteria,[1-4,16-25,36-39] and no multiple publications were found. Agreement between reviewers regarding selection of relevant articles was 100%. A total of 10 articles were excluded[26-35]: 10 articles met the exclusion criteria, 4 used protease inhibitors in both groups,[26-29] and 2 evaluated nonclinical outcomes,[30,31] 2 review,[32,33] 1 comment,[34] and 1 postoperative study.[35] We therefore analyzed 18 articles with a total of 4966 subjects (Online Table 1, available at www.giejournal.org, and Fig. 1).