資料編

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Management and Treatment of Osteoporosis in Patients Receiving Long-term Glucocorticoid Treatment: Current Status of Adherence to Clinical Guidelines and Related Factors

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Abstract

Objective The aim of this study was to evaluate the adherence of guidelines for the management and treatment of glucocorticoid-induced osteoporosis, and to investigate whether it is associated with factors such as age, gender, glucocorticoid dose, physician specialty, and size of facility.

Methods This was a cross-sectional study utilizing administrative data from a database of health insurance claims (2004-2007); 2,368 patients who received glucocorticoid treatment for≥90 days were extracted. The guideline adherence was determined by evaluations based on glucocorticoid prescription dose, prescription of anti-osteoporosis drugs, and whether or not bone mineral density was measured.

Results Overall proportion of guideline adherence was 23.3%. In cases in which the equivalent dose of prednisolone was<5 mg/d and≥5 mg/d, the adherence was 8.3% and 30.5% respectively. Factors correlating with low adherence included young age, male gender, and lower glucocorticoid doses. Surgery and otolaryngology specialties had lower adherence than internal medicine. Smaller clinical facilities had lower adherence than larger facilities.

Conclusion The adherence of guidelines for the management and treatment of glucocorticoid-induced osteoporosis is still low, and improvements in treatment quality can be expected through education of patient groups and medical care providers with large deviations from the guidelines.

Key words: clinical guidelines, glucocorticoid-induced osteoporosis, guideline adherence

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Introduction

Glucocorticoids are used widely for their strong anti-inflammatory and immunosuppressive effects. There are many side effects to long-term glucocorticoid use, an important one of which is osteoporosis and subsequent bone fracture (1-3). A 1996 study by the American College of Rheumatology revealed that 20% of osteoporosis patients in the U.S. were induced by glucocorticoids and that 25% of patients under long-term glucocorticoid treatment had bone fractures (4). It has been reported that the risk of new vertebral fractures reaches its peak at 3-6 months after initiation of oral glucocorticoid treatment (5), and the importance of early management has been recognized.

Since 1996, the efficacy of anti-osteoporosis drugs has been reported in some large-scale clinical trials (6). The efficacy of drugs used to treat glucocorticoid-induced osteoporosis (GIOP) has also been established. Specifically, bisphosphonates are effective in preventing and treating bone loss in GIOP patients (7-9). Although less effective, activated vitamin D_3 and vitamin K_2 also have been reported to prevent bone fractures (10, 11). In the U.S. and Europe, management guidelines for GIOP were published in

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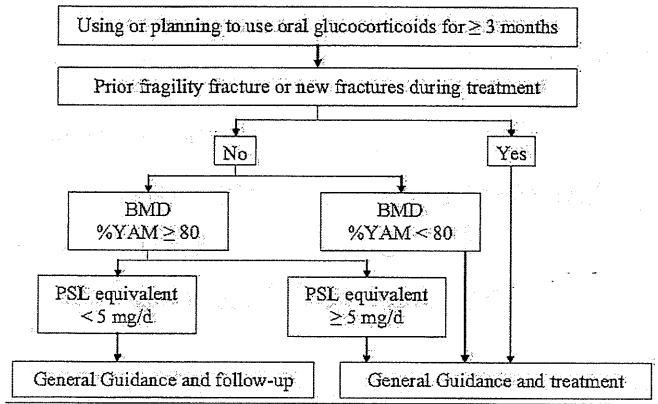

-General guidance
Lifestyle guidance, nutritional guidance and exercise therapy are based on those for primary osteoporosis
-Follow-up observation (routine monitoring)
Bone mineral density measurements and X-ray of the thoracolumbar spine are performed on a regular basis (every 6 months to 1 year)
-Drug treatment anti-osteoporosis drug therapy
1. Bisphosphonates are first-line drugs
2. Activated vitamin D_3 and vitamin K_2 are second-line drugs

YAM: the Young Adult Mean (20-44 years old)
BMD: Bone Mineral Density
PSL: prednisolone
These guidelines cover a patient ≥18 years of age
Definition of fragility fractures is the same as that for primary osteoporosis
BMD measurements are based on those for primary osteoporosis (2000 revised edition)

Figure 1. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis in Japan (2004 edition) (13).

1996 (3, 12) and have since been revised. In Japan, the "Guidelines for the Management and Treatment of Glucocorticoid-induced Osteoporosis" was released for the first time in 2004 (13). The guidelines apply to patients 18 years of age or older who are using or planning to use oral glucocorticoids for≥3 months, and they emphasize management and treatment from an early stage (Fig. 1).

After the release of the guidelines in Japan, no large-scale study on the state of adherence to guidelines in clinical practice has been conducted. Since glucocorticoids are used widely regardless of specialty, adherence to the guidelines may differ among specialties. In addition, osteoporosis is more frequently seen in postmenopausal women and the elderly (14), thus management and treatment may not be sufficiently conducted for males or young patients under long-term glucocorticoid treatment. In order to improve osteoporosis treatment, various trials have been conducted, some of which have been effective (15, 16). On the other hand, the previous trials on GIOP have shown low efficacies (17, 18), and it is important to know what characteristics of the patient and clinical setting should be intervened.

It has recently become clear that there is a discrepancy between clinical evidence and actual practice (19, 20). Improving the quality of clinical practice requires not only determining evidence, but also implementing the means to improve this evidence. The propagation of a recommended treatment through clinical guidelines is one method of disseminating evidence (21). Investigation of how well guidelines are adhered to and the factors related to adherence will aid in recognizing the deviation of actual clinical practice from the guidelines. We used a database of health insurance claims (receipts) to study adherence to guidelines for the management and treatment of GIOP, and its relation to factors such as age, gender, glucocorticoid dose, physician specialty, and facility size.

Materials and Methods

Study design

The Japan Medical Data Center Co., Ltd (JMDC) (22) has constructed and run a database of health insurance claims data from health insurance unions in Japan: JMDC-MDB (medical database). This database includes 530,000 cumulative insured persons, mainly company employees and their family members, from January 2004 to December 2007. Individuals who fulfilled the criteria for the guidelines were selected from the JMDC-MDB and a cross-sectional study was carried out.

Participants

This study utilized cases in which oral glucocorticoids were prescribed continuously for≥90 days. We extracted cases from the JMDC-MDB that included at least 3 months of treatment in which oral glucocorticoids were prescribed for at least 28 days during the study period and in which the

- Patients taking <5 mg/d PSL equivalent
  - A) Prescription of anti-osteoporosis drugs (drug therapy) (Drug therapy was assumed to be initiated due to a history of fragility fracture or BMD value)
  - B) Routine measurement of BMD (monitoring)
- Patients taking ≥5 mg/d PSL equivalent
  - C) Prescription of anti-osteoporosis drugs (drug therapy)

Figure 2. Standards for determining adherence to the guidelines.

patient was 18 years of age or older. Of these cases, exclusion criteria were those in which the prescription was continuous for<90 days; hypopituitarism or adrenal gland dysfunction necessitated supplementation of adrenocortical hormones; special conditions such as palliative care were thought to be due to malignant tumors and the prescribed dose of glucocorticoids was unclear.

The background information obtained from the JMDC-MDB for each participant included year of birth, gender, details of oral glucocorticoid prescriptions, physician specialty, and facility size. The prescribed dose of glucocorticoids was calculated by converting the dose to the equivalent of prednisolone (PSL). When the dose changed during the course of the treatment, the maximum mean dose of 90 continuous days was used. When oral glucocorticoids were prescribed by physicians in multiple specialties, the specialty which was primarily responsible for prescribing glucocorticoids was used. Facility size was divided into four groups: clinic (0-19 beds), small hospital (20-199 beds), medium-sized hospital (200-499 beds), and large hospital (≥500 beds).

Measurement of adherence to guidelines

Adherence to guidelines was used as the main outcome measurement. According to the flowchart in the guidelines (Fig. 1), anti-osteoporosis drug therapy is recommended for patients with previous fragility fractures, patients who had a bone fracture occur during treatment, and those in whom bone mineral density (BMD) was<80% of the young adult mean (YAM). The guidelines list bisphosphonates as the drugs of choice for this treatment, with activated vitamin D_3 or vitamin K_2 as alternatives. Since the disease name on the health insurance claims did not always represent the actual disease and they lacked information on results of medical tests performed, adherence to guidelines in this study was evaluated based on glucocorticoid prescription dose, prescription of anti-osteoporosis drugs, and whether or not BMD was measured (Fig. 2).

Bone fracture risk increases dose-dependently with glucocorticoids, and it has been reported that 5 mg/d PSL is the threshold dose beyond which bone fracture risk increases (5). Consequently, the Japanese guidelines recommend routine monitoring (every 6 months to 1 year) by BMD measurement and X-ray of the thoracolumbar spine for patients taking<5 mg/d PSL, and drug therapy regardless of BMD value if the PSL dose is≥5 mg/d. In cases in which an anti-osteoporosis drug was prescribed during glucocorticoid treatment with<5 mg/d PSL, it was assumed that prescription of anti-osteoporosis drugs was initiated due to a prior fragility fracture or low BMD measurements, and it was considered as adherence to guidelines (Fig. 2, A). When anti-osteoporosis drugs were not prescribed, routine monitoring of BMD as adherence to guidelines was considered (Fig. 2, B). In cases in which the PSL dose was≥5 mg/d, prescription of an anti-osteoporosis drug during glucocorticoid treatment was considered as adherence to guidelines (Fig. 2, C).

Statistical analysis

First, the number of participants in this study was determined and characteristics of the patient (gender, age, and glucocorticoid dose) and of the clinical setting (physician specialty and facility size) were noted. Male and female patient attributes were compared by using the chi-square test and t-test. Adherence to the guidelines was determined based on glucocorticoid dose, prescription of anti-osteoporosis drugs, and BMD measurement. A univariate analysis was performed to determine the correlation between adherence to the guidelines and five factors (gender, age, glucocorticoid dose, physician specialty, and facility size). Next, multiple logistic regression analyses were performed using adherence to the guidelines as the dependent variable and each factor as the independent variable. Furthermore, cases were divided into two groups based on PSL dose (≥5 mg/d or<5 mg/d) since guideline adherence standards are different for these two groups were divided, and a stratified analysis was performed. Stratified analyses by gender, age and facility size were also performed. Differences were considered to be statistically significant at $p<0.05$ for all statistical tests. All analyses were performed using STATA version 11 (Stata Corp., College Station, TX, USA).

This study was approved by the Ethics Committee, Kyoto University Graduate School of Medicine.

Results

Initial search was matched criteria of a patient≥18 years of age for whom oral glucocorticoids were prescribed for≥28 days/month for≥3 months during the study period, and

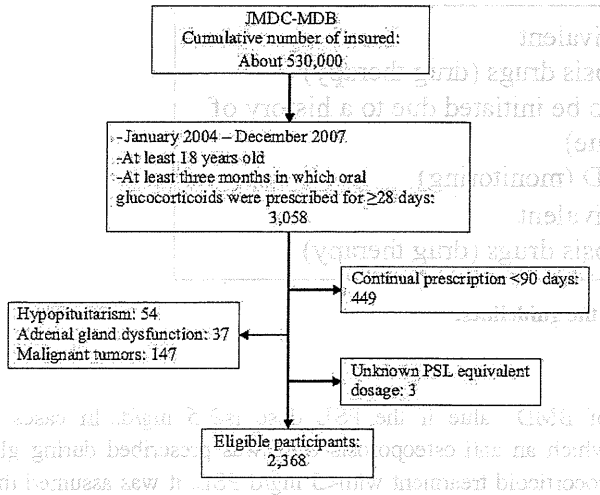

Figure 3. Flowchart for the selection of study participants.

3,058 cases were found. Among these cases, 449 patients who were not prescribed continually for≥90 days, 54 patients with hypopituitarism, 37 with adrenal gland dysfunction, 147 with suspected malignant tumors, and 3 with unknown glucocorticoid dose were excluded. The remaining 2,368 patients were included as the present participants (Fig. 3).

Characteristics of participants

Table 1 summarizes the characteristics of the 2,368 eligible participants. Mean age was 45.9 years (range: 19-98 years), and 53.5% of participants were female. Mean dose of glucocorticoids was 6.6 mg/d PSL equivalent, and the dose was<5 mg/d for approximately one-third of the cases. The majority of physicians prescribing glucocorticoids were in the internal medicine specialty group (57.4%). Approximately half of the facilities were clinics (0-19 beds). In 22.9% of the cases, the first or second choice osteoporosis medication was prescribed during glucocorticoid treatment. In some cases, multiple osteoporosis drugs were prescribed, but activated vitamin D_3 was the predominantly prescribed drug and vitamin K_2 was seldom prescribed. BMD was measured in only 4.7% of patients not receiving osteoporosis treatment, revealing its infrequent use as a monitoring method. Gender comparison revealed that males were significantly younger than female participants ($p<0.001$). The majority of participants that received glucocorticoid prescriptions from internal medicine and orthopedic specialists were female, while those participants who were prescribed glucocorticoids by physicians in dermatology and otolaryngology were predominantly male. More males were treated in clinics and more females were treated in large hospitals. Males were significantly less likely to receive osteoporosis treatment and BMD measurement.

Table 2 shows the treated underlying diseases according to physician specialty. The main three diseases, allergic rhinitis, rheumatoid arthritis and atopic dermatitis, constituted up to half of the overall underlying diseases. The most common disease was rheumatoid arthritis for orthopedic surgery, and allergic rhinitis for otolaryngology. In the other physician specialties, there were various underlying diseases.

Main analysis

Adhering to the guidelines was a total of 551 cases (23.3%). Amongst the patients taking an equivalent of<5 mg/d PSL, 64 cases (8.3%) were adhering to the guidelines (Table 3). These cases included 56 patients (7.3%) who received osteoporosis medication during glucocorticoid treatment and 8 patients (1.0%) who were not prescribed osteoporosis medication, but had routine BMD measurements (every 6 months to 1 year). Among these patients taking≥5 mg/d PSL, 487 cases (30.5%) in which osteoporosis medications were prescribed during glucocorticoid treatment were classified as adhering to the guidelines.

The adherence for each factor and odds ratios (ORs) before and after adjustment by logistic regression was calculated (Table 4). The adjusted odds ratio (AOR) was higher in females and increased with age. Glucocorticoid dose was divided into groups of 5 mg increments and each group was evaluated separately. ORs decreased after adjustments, but increased dose-dependently. Differences among specialties were observed, and ORs were smaller for surgery and otolaryngology compared to internal medicine. ORs were larger for larger facilities, despite the decrease after adjustment. Due to a small amount of missing data, a sensitivity analysis was not performed.

Subgroup analysis

Stratified analysis was performed by dividing patients into those taking ≥5 mg/d PSL and those taking <5 mg/d PSL, and calculating AOR for each group (Table 5). In cases with PSL dose <5 mg/d, OR was greater for females, physicians in the orthopedic specialty, and small-scale hospitals, while ORs tended to be smaller for otolaryngology and dermatology specialists. In cases with PSL dose ≥5 mg/d, results were similar, except for the lack of a significant difference in otolaryngology.

General knowledge that osteoporosis frequently occurs after menopause may increase clinicians' attitude for providing examination and treatment. Therefore, stratified analysis was performed based on gender and the possibility of menopause, with a cut-off age of 50 years old (Table 6). For male, ORs tended to be much larger as the prescribed dose of glucocorticoids increased regardless of the age compared with females. For females, the influence of facility size was less in the older group than in the younger one.

Due to the lack of examination resources, measuring BMD is difficult to do at clinics relative to medium-sized or large hospitals. Stratified analysis based on facility size showed that female or older patients were more likely to be treated according to guidelines' recommendation at clinics (Table 7).

Table 1. Characteristics of Participants

	Total n=2,368	Males n=1,100	Females n=1,268
Mean age, year ± SD	45.9±13.4	44.4±12.9	47.3±13.8
Gender, male (%)	1100 (46.5)		
Glucocorticoid dose (%)			
PSL <5 mg/d	772 (32.6)	364 (33.1)	408 (32.2)
PSL ≥5 mg/d	1596 (67.4)	736 (66.9)	860 (67.8)
Physician specialty (%)			
Internal medicine	1359 (57.4)	577 (52.5)	782 (61.7)
Surgery	176 (7.4)	92 (8.4)	84 (6.6)
Orthopedic surgery	237 (10.0)	72 (6.5)	165 (13.0)
Dermatology	365 (15.4)	107 (9.7)	86 (6.8)
Otolaryngology	193 (8.2)	234 (21.3)	131 (10.3)
Other specialties	38 (1.6)	18 (1.6)	20 (1.6)
Facility size (%)			
Clinic	1204 (50.8)	598 (54.4)	606 (47.8)
Small hospital	145 (6.1)	69 (6.3)	76 (6.0)
Medium-sized hospital	265 (11.2)	112 (10.2)	153 (12.1)
Large hospital	754 (31.8)	321 (29.2)	433 (34.1)
Anti-osteoporosis drug (%)			
Bisphosphonates	286 (12.1)	57 (5.2)	229 (18.1)
Activated vitamin D_3	337 (14.2)	99 (9.0)	238 (18.8)
Vitamin K_2	49 (2.1)	16 (1.5)	33 (2.6)
Other	101 (4.3)	16 (1.5)	85 (6.7)
First or second choice treatment	543 (22.9)	144 (13.1)	399 (31.5)
BMD measurement (%)			
During osteoporosis treatment	194/543 (35.7)	33/144 (22.9)	151/399 (37.8)
Before osteoporosis treatment	86/1825 (4.7)	21/956 (2.2)	65/869 (7.5)

Facility size: clinic (0-19 beds), small hospital (20-199 beds), medium-sized hospital (200-499 beds), and large hospital (≥500 beds)

Table 2. Treated Underlying Disease of Each Physician Specialty (The Main Three Diseases)

Physician specialty (N)	The main three diseases (N)		
Overall (2368)	Allergic rhinitis (463)	Rheumatoid arthritis (407)	Atopic dermatitis (183)
Internal medicine (1359)	Allergic rhinitis (218)	Rheumatoid arthritis (209)	SLE (144)
Surgery (176)	Allergic rhinitis (31)	After the organ plant (25)	Atopic dermatitis (16)
Orthopedic surgery (237)	Rheumatoid arthritis (188)	Allergic rhinitis (10)	Bronchial asthma (5)
Otolaryngology (193)	Allergic rhinitis (162)	Bronchial asthma (14)	Sudden deafness (4)
Dermatology (365)	Atopic dermatitis (125)	Urticaria (52)	Allergic rhinitis (24)

Table 3. Guideline Adherence

	Guideline adherence N (%)
Total	551/2368 (23.3)
PSL <5mg/d	64/772 (8.3)
PSL ≥5mg/d	487/1596 (30.5)

Discussion

The overall proportion of adherence of 23.3% in this study was low compared to a U.S. study, in which the recommended acute, chronic, and preventative treatment was performed in about 50% of cases (19). The adherence was particularly low for cases with PSL dose <5 mg/d and routine monitoring by BMD measurement was rarely performed. When prescribing glucocorticoids for a long period, even in low dosages, physicians should take measures to monitor for potential osteoporosis. Proportion of adherence to the guidelines was 30.5% for cases in which anti-osteoporosis drug therapy is recommended (PSL dose ≥5 mg/d). In the U.S., where guidelines were implemented in 1996, the frequency of BMD measurement among patients receiving glucocorticoids in 2001-2003 increased to about triple compared with 1995-1998, and prescription of bisphosphonates increased to double or triple (23). In other countries as well, treatment of GIOP has improved in recent years (24). The proportion of patients receiving drug therapy is still low in Japan compared to the U.S., but an increase can be expected if the guidelines are propagated.

Factors associated with a high adherence in this study in-

Table 4. Odds Ratio (before and after Adjustment) for Each Factor

	Guideline adherence N (%)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age			
10 year increase		1.25 (1.17-1.34)	1.36 (1.25-1.48)
Gender			
Male	145/1100 (13.2)	1	1
Female	406/1268 (32.0)	3.10 (2.51-3.85)	3.46 (2.70-4.43)
Glucocorticoid dose			
<5 mg/d	64/772 (8.3)	1	1
≥5, <10 mg/d	217/1014 (21.4)	3.01 (2.23-4.11)	2.10 (1.52-2.91)
≥10, <15 mg/d	149/368 (40.5)	7.53 (5.35-10.63)	5.49 (3.76-8.03)
≥15 mg/d	121/214 (56.5)	14.40 (9.76-21.25)	10.15 (6.55-15.73)
Physician specialty			
Internal medicine	414/1359 (30.5)	1	1
Surgery	17/176 (9.7)	0.24 (0.14-0.41)	0.28 (0.16-0.48)
Orthopedic surgery	61/237 (25.7)	0.79 (0.57-1.09)	1.30 (0.91-1.88)
Otolaryngology	5/193 (2.6)	0.06 (0.02-0.14)	0.27 (0.11-0.69)
Dermatology	50/365 (13.7)	0.36 (0.26-0.50)	0.81 (0.56-1.18)
Facility size			
Clinic	99/1204 (8.2)	1	1
Small hospital	41/145 (28.3)	4.40 (2.83-6.77)	2.77 (1.75-4.38)
Medium-sized hospital	101/265 (38.1)	6.87 (4.92-9.60)	3.86 (2.70-5.53)
Large hospital	310/754 (41.1)	7.79 (6.03-10.12)	4.88 (3.67-6.50)

Table 5. Stratified Analysis Based on Glucocorticoid Dose (Adjusted Odds Ratio)

	PSL <5 mg/d (95% CI) n=772	PSL ≥5 mg/d (95% CI) n=1,596
Age		
10 year increase	1.37 (1.11-1.70)	1.36 (1.24-1.49)
Gender		
Male	1	1
Female	8.37 (3.45-20.34)	3.15 (2.42-4.09)
Physician specialty		
Internal medicine	1	1
Surgery	0.31 (0.04-2.40)	0.28 (0.16-0.49)
Orthopedic surgery	2.01 (1.01-4.01)	1.11 (0.72-1.72)
Otolaryngology	0.13 (0.02-0.98)	0.41 (0.14-1.22)
Dermatology	0.53 (0.20-1.44)	0.91 (0.60-1.38)
Facility size		
Clinic	1	1
Small hospital	5.29 (1.97-14.19)	2.38 (1.42-4.00)
Medium-sized hospital	2.39 (0.92-6.21)	4.07 (2.74-6.06)
Large hospital	4.24 (2.17-8.28)	4.93 (3.57-6.80)

cluded old age, female gender, and larger doses of glucocorticoids. In particular, the implementation of guidelines' recommendation was sharply improved as prescribed dose of glucocorticoids increased in male. The influence of facility size was less in the older female group than in the younger group. It may be because clinicians at the clinic know the number of patients with menopausal osteoporosis increases with aging and they tended to implement guidelines' recommendation for older females even at clinics. On the other hand, attention towards the guidelines for young patients and males who receive long-term glucocorticoid treatment should be promoted to minimize the lack of appropriate treatment for these patients. In terms of physician specialty, the adherence was lower in surgery and otolaryngology compared to internal medicine. These specialties see fewer cases of osteoporosis, thus emphasis should be made to increase guideline awareness. Smaller facilities also showed lower adherence. Factors such as difficulty of immediate access to other specialties or clinical tests like BMD measurement may be possible reasons. Stratified analysis based on facility size showed that female or older ones were more likely to be treated according to guidelines' recommendation at clinics. Similar findings were obtained when stratified analyses were performed considering menopause; the cut-off age was 50 years old in the present study. Stratified analysis based on glucocorticoid dose showed some differences between PSL dose ≥5 mg/d and <5 mg/d. In the PSL dose <5 mg/d, trends of these cases were likely similar to those of cases of anti-osteoporosis treatment in the entire population since PSL equivalent glucocorticoid doses were low.

Although the receipt database is not research-oriented, such a database can be useful for research if its limitations (for example, the underlying disease name is unclear, and it is not understood whether it is facilities where BMD measurement is possible) are well understood. JMDC-MDB comprises data only from several health insurance unions, and its patient population is younger than the general patient population in Japan and sampling bias of participants is possible. Moreover, the present study is a simple cross-sectional study examining four years as a whole, so the differences of period of participants' adherence to guidelines were not considered. Many clinical guidelines have been instituted in the past decade in Japan (25, 26). However, there have been few reports on how well these guidelines have been followed. By using the receipt database, investigations of actual treatments in relation to other clinical guidelines, and long-term

Table 6. Stratified Analysis by Gender and Age Group (Adjusted Odds Ratio)

	Male, Age <50 (95% CI) n=693	Male, Age ≥50 (95% CI) n=407	Female, Age <50 (95% CI) n=721	Female, Age ≥50 (95% CI) n=547
Glucocorticoid				
<5 mg/d	1	1	1	1
≥5, <10 mg/d	6.70 (1.51-29.79)	4.06 (1.21-10.98)	1.66 (0.93-2.96)	1.67 (1.05-2.66)
≥10, <15 mg/d	13.28 (2.92-60.52)	6.39 (1.72-19.32)	4.45 (2.33-8.54)	5.89 (3.10-11.22)
≥15 mg/d	34.17 (7.28-160.4)	10.56 (2.94-38.02)	8.52 (4.16-17.46)	4.94 (1.87-13.12)
Physician specialty				
Internal medicine	1	1	1	1
Surgery	0.20 (0.05-0.91)	0.60 (0.21-1.77)	0.27 (0.11-0.69)	0.17 (0.06-0.51)
Orthopedic surgery	1.16 (0.13-10.59)	0.73 (0.23-2.36)	1.82 (0.95-3.48)	1.16 (0.71-1.92)
Otolaryngology	0.92 (0.19-4.49)	0.67 (0.08-5.66)	0.28 (0.06-1.36)	0.13 (0.02-0.97)
Dermatology	1.84 (0.89-2.29)	0.63 (0.24-1.70)	0.76 (0.39-1.52)	0.49 (0.22-1.09)
Facility size				
Clinic	1	1	1	1
Small hospital	4.37 (1.11-17.30)	1.97 (0.53-7.41)	5.08 (1.98-13.05)	2.52 (1.27-4.99)
Medium-sized	9.40 (3.44-25.74)	4.92 (1.79-13.54)	8.13 (4.16-15.89)	1.59 (0.90-2.83)
Large hospital	10.12 (4.38-23.39)	7.17 (3.05-16.91)	7.07 (4.10-12.20)	2.66 (1.68-4.22)

Table 7. Stratified Analysis Based on Facility Size (Adjusted Odds Ratio)

	Clinic (95% CI) n=1204	Medium-sized and Large hospital (95% CI) n=1019
Age		
10 year increase	1.87 (1.56-2.25)	1.19 (1.07-1.31)
Gender		
Male	1	1
Female	5.42 (2.95-9.96)	2.77 (2.07-3.70)
Glucocorticoid dose		
<5 mg/d	1	1
≥5, <10 mg/d	1.70 (0.99-2.92)	2.40 (1.51-3.82)
≥10, <15 mg/d	6.85 (3.26-14.42)	5.45 (3.27-9.09)
≥15 mg/d	32.74 (9.98-107.3)	9.55 (5.52-16.52)
Physician specialty		
Internal medicine	1	1
Surgery	0.28 (0.08-0.99)	0.29 (0.16-0.53)
Orthopedic surgery	2.05 (1.19-3.56)	0.95 (0.57-1.59)
Otolaryngology	0.23 (0.06-0.99)	0.42 (0.12-1.56)
Dermatology	0.52 (0.23-1.19)	1.11 (0.71-1.75)

changes in treatment may be possible.

Although the guidelines list the first and second choice treatments for drug therapy, the efficacy of two groups is very different (27, 28). After the issuance of the guideline in Japan, there came some promising drugs. Teriparatide, a recombinant human parathyroid hormone, is more effective in increasing BMD than alendronate, a bisphosphonate, and the prescription for high risk patients (postmenopausal women and men age ≥50 years) is recommended by American College of Rheumatology 2010 (29, 30). The present study investigated the adherence to the current Japanese guidelines published in 2004, but guidelines will be revised considering new evidence in the near future.

The present findings revealed that the current state of the management of osteoporosis in patients receiving chronic glucocorticoid therapy in Japan was found to be unsatisfactory in terms of established evidence. Potential factors for low adherence included young age, male gender, lower glucocorticoid dose, prescription by surgery and otolaryngology specialists, and smaller clinical facilities. The most common barriers in the adherence to the guideline are the provider factor, the patient factor, and the system factor (31). For example, poor knowledge is included in provider barriers, nonadherence is included in patient barriers, and obtaining DXA and computerized ordering system are included in system barriers. Provider education, patient educational handouts and computerized clinical reminders are suggested for guideline adherence improvement. Improvements in treatment quality can be expected by educating particular characteristic factors of the patients and the clinical settings associated with large deviations from guideline recommendations.

The authors state that they have no Conflict of Interest (COI).

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2012年2月1日
日本消化器病学会診療ガイドライン
ワーキンググループ・ワークショップ

メタアナリシス／システマティックレビューから総意形成による推奨度決定：GRADE法の試行

京都大学大学院医学研究科
社会健康医学系専攻健康情報学分野
中山健夫

2012年2月1日
日本消化器病学会診療ガイドライン
ワーキンググループ・ワークショップ

Treatment of acute pancreatitis with protease inhibitors: an updated meta-analysis

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京都大学大学院医学研究科 健康情報学 中山健夫

Introduction

- 急性膵炎は突然の腹痛、膵酵素上昇、画像異常によって規定
- 急性膵炎の転帰は一般に良好で、十分な輸液を中心とした保存的治療で改善
- 急性膵炎による全入院患者の死亡率は10%
  - 重症膵炎では30%を超える
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Introduction

- 急性膵炎の治療
  - 十分な輸液
  - 適切な鎮痛剤の使用は疼痛を効果的に軽減し、診療や治療の妨げにならない(Brownfield E, 2001)
  - H2RAの併用はメタ分析の手法で否定的
    (Morimoto T, Noguchi Y, et al. Eur J Gastroenterol Hepatol 2002)
- タンパク分解酵素阻害剤の治療効果についてメタ分析で検討
  (Seta T, Noguchi Y,et al. Eur J Gastroenterol Hepatol 2004)
- 軽度の急性膵炎ではタンパク分解酵素阻害剤による死亡率の抑制は示されず
  (pooled risk difference, -0.03; 95% CI, -0.07 to 0.01).
- 対照群死亡率10%以上の中等度から重症急性膵炎では、やや有効
  (pooled risk difference, -0.07; 95% CI, -0.13 to -0.01)
  - その真の効果は様々なバイアスの存在で優劣判定が困難
    - 研究の質、患者背景、重症度の評価や記載法が異質
- 新たなRCTsを加えてメタ分析を更新し、タンパク分解酵素阻害剤の効果を再検証する

Methods

- Meta Analysis
  - –Literature Search
  - –Inclusion and Exclusion Criteria
  - –Outcome Measures
  - –Quality Assessment for Primary Studies
  - –Statistical Analysis

Methods

- 検索した媒体
  - – MEDLINE、EMBASE、コクランデータベース、医中誌
- 検索期間
  - – 1965年1月から2011年12月まで
- キーワード
  - – 膵炎（Pancreatitis）、タンパク分解酵素阻害剤（Protease inhibitors）
- 研究様式はRCT
- 言語制限なし
- 同テーマの先行メタ分析や通読対象となった全RCTの参考文献リストを通読、必要があれば一次文献を入手して通読
- 臨床試験登録システム（UMIN、JMACCT、JAPIC、ClinicalTrials.gov）で本研究に該当するRCTの存在を確認

Methods

- 包含条件
  - –急性膵炎を研究対象
  - –急性膵炎の重症度による除外は設けなかった
  - –タンパク分解酵素阻害剤の種類による制限は設けなかった
  - –介入群にタンパク分解酵素阻害剤を、対照群にプラセボを投与したRCTのみ
  - –性別、年齢による制限は設けなかった

Methods

- 除外条件
  - – 両群にタンパク分解酵素阻害剤を経静脈投与した研究
  - – タンパク分解酵素阻害剤を経動脈投与もしくは腹腔内に投与した研究
  - – 慢性膵炎患者を研究対象とした研究
  - – ERCP後膵炎の研究
  - – 凍結血漿を投与した研究
  - – 基礎医学研究
  - – HIV感染患者を対象とした研究
  - – 抗菌薬の効果を検討した研究
  - – 術後膵炎患者を対象とした研究
  - – 経口投与した研究
  - – この他、研究者間で不適当と判断した研究

Methods

- アウトカム測定
  - メインアウトカムはタンパク分解酵素阻害剤投与による急性膵炎による死亡の抑制効果
- この他のアウトカム
  - 疼痛緩和効果
  - 膵炎後仮性嚢胞形成抑制効果
  - 腹腔内膿瘍形成抑制効果
  - 手術回避の効果
  - 腸閉塞抑制効果
  - 1つ以上の合併症(例えば多臓器不全)発生抑制効果

Quality Assessment for Primary Studies

Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.

	なし	あり
ランダム化の記載	0	1
具体的なランダム化の記載	0	1
二重盲検化の記載	0	1
具体的な二重盲検化の記載	0	1
脱落の有無の記載	0	1

最低点　0点、最高点　5点で各RCTの質を評価

本研究では、Jadad score 3点以上をHigh Quality Studyとみなした

Methods

- データ抽出
  - 主研究者以外の共同研究者が独立して共通の抽出基準で文献検索を実施
  - 続いて選択法を使用して最終包含研究を選択
  - 共通認識の下でデータを抽出
  - 研究参加者が全結果を持ち寄り、合議に至るまで結果をすりあわせ
  - 結果に相違があれば、その原因について議論

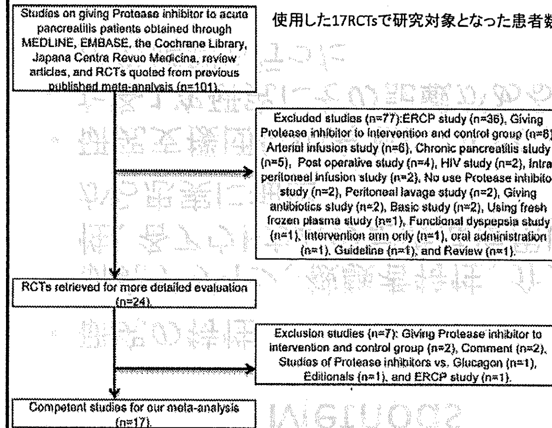
Methods

- 研究の特性
- 研究デザイン、被験者特性、介入の特性、各アウトカムの定義は使用したRCTから忠実に抽出
- 研究支援団体の有無について、使用した各1次研究にその記載があるかどうかの確認も行った

Statistical Analysis

- 各アウトカムの発生頻度の差（リスク差、Risk Difference, RD）とその95%信頼区間を計算
- 各計算結果をメタ分析の手法で統合(Pooled RD)
- 各研究のリスク差にばらつき（均一さ、Homogeneity ）が統計学的に存在した場合、存在しない場合で異なる統計処理方法を使用
  - Mantel-Haenszel法、DerSimonian-Laird (D-L) 法
- 得られたリスク差から、NNT(Numbers needed to treat, NNT)を計算
  - NNT= 1/risk difference
  - 1人に転帰が起きることを予防するために治療を要する患者数
- 統計処理はSTATA statistical softwareを使用
- 結果は、平均と95%信頼区間で示し、p<0.05で統計学的有意

使用した17RCTsで研究対象となった患者数は総数で1697人



Flow of randomized controlled trials through the process of retrieval and inclusion in the meta-analysis comparing protease inhibitors with placebo for acute pancreatitis.

Table 1 Characteristics of primary studies

Author	Year	Setting	Publication type	Masking	Country	Language	Treatment of: Intervention	Control	Design	Definition of acute pancreatitis	Method of protease inhibitors administration
Skyring A	1965	Single	Full paper	Double blind	Australia	English	Aprotinin	Placebo	Prospective	Elevated serum amylase levels (>500 Somogyi units/dl) and plain X-ray film of the abdomen or laparotomy	Intravenous
Ryall RJ	1966	Single	Full paper	Open	England	English	Aprotinin	Placebo	Prospective	Elevated serum amylase levels (>500 Somogyi units/dl) and plain X-ray film of the abdomen or laparotomy	Intravenous
Trapnell JE	1967	Multicenter	Full paper	Double blind	England	English	Aprotinin	Placebo	Prospective	Elevated serum amylase levels (>1000 Somogyi units/dl) or the findings of pancreatitis at [illegible]	Intravenous
Bachrach WH	1968	Multicenter	Full paper	Double blind	USA	English	Aprotinin	Placebo	Prospective	No mention	Intravenous
Moller C	1969	Single	Full paper	Open	Finland	Germany	Aprotinin	Placebo	Prospective	Abdominal pain with elevating urinary diastase concentration and/or lipase	Intravenous
Baden H	1969	Multicenter	Full paper	Double blind	Denmark	English	Aprotinin	Placebo	Prospective	Elevating urinary diastase concentration	Intravenous
Trapnell JE	1974	Multicenter	Full paper	Double blind	England	English	Aprotinin	Placebo	Prospective	Either a consistent clinical picture, together with a serum amylase in excess of 1000 Somogyi units, or [illegible]	Intravenous
MRC Multicenter Trial	1977	Multicenter	Full paper	Double blind	England	English	Aprotinin	Placebo	Prospective	Serum amylase of at least 2000 IU/l or the finding of acute pancreatitis at [illegible]	Intravenous
Gauthier A	1978	Multicenter	Full paper	Double blind	France	French	Aprotinin	Placebo	Prospective	No mention	Intravenous
Imrie CW	1978	Single	Full paper	Double blind	England	English	Aprotinin	Placebo	Prospective	Clinical presentation and the presence of hyperamylasaemia in excess of 1200 IU/l and similar elevations in [illegible]	Intravenous
MRC Multicenter Trial	1980	Multicenter	Full paper	Double blind	England	English	Aprotinin	Placebo	Prospective	[illegible] in excess of 2000 IU/l or the finding of acute pancreatitis at [illegible]	Intravenous
Freise J	1986	Multicenter	Full paper	Double blind	German	Germany	Gabexate Mesilate	Placebo	Prospective	No mention	Intravenous
Yang CY	1987	Single	Full paper	Open	China	English	Gabexate Mesilate	Placebo	Prospective	Raised serum amylase level, amylase creatinine clearance ratio, and serum lipase level in addition to abdominal pain and [illegible]	Intravenous
Goebell H	1988	Multicenter	Abstract	Unclear	German	English	Gabexate Mesilate	Placebo	Prospective	No mention	Intravenous
Valderrama R	1992	Multicenter	Full paper	Double blind	Spain	English	Gabexate Mesilate	Placebo	Prospective	Upper abdominal pain with a serum amylase level of more than twice the upper limit of [illegible]	Intravenous
Buchler M	1993	Multicenter	Full paper	Double blind	Germany	English	Gabexate Mesilate	Placebo	Prospective	Upper abdominal pain with a serum amylase level of more than three times the upper limit of normal	Intravenous
Chen HM	2000	Single	Full paper	Open	Taiwan	English	Gabexate Mesilate	Placebo	Prospective	Upper abdominal pain with a serum amylase level of more than three times the upper limit of [illegible]	Intravenous

APACHE, Acute Physiology and Chronic Health Evaluation; UN, Unobtainable data from published work

Author	Description of: Main outcome in methods	Basis of sample size calculation in methods	Patient numbers of: Intervention	Control	Mean age of: Intervention	Control	Grant: Fund was supplied by sponsor	Medicine was supplied by sponsor	Ranson's score: Intervention	Control
Skyring A	No	No	11	12	60.4	60.8	No	Yes	UN	UN
Ryall RJ	No	No	18	16	64	68	No mention		UN	UN
Trapnell JE	No	No	26	24	61.5	61.6	No	Yes	UN	UN
Bachrach WH	No	No	45	54	UN	UN	No	Yes	UN	UN
Moller C	No	No	43	45	UN	UN	No mention		UN	UN
Baden H	No	No	20	21	58	54	No mention		UN	UN
Trapnell JE	No	No	53	52	UN	UN	No	Yes	UN	UN
MRC Multicenter Trial	No	No	88	125	UN	UN	No	Yes	UN	UN
Gauthier A	Yes	No	38	25	56.2	48.1	No mention		UN	UN
Imrie CW	No	No	80	81	51.4	61.4	Yes	Yes	UN	UN
MRC Multicenter Trial	Yes	No	99	110	UN	UN	No	Yes	UN	UN
Freise J	No	No	50	50	UN	UN	No	Yes	UN	UN
Yang CY	No	No	21	31	47	47	No	Yes	UN	UN
Goebell H	No	No	78	78	UN	UN	No mention		UN	UN
Valderrama R	No	No	51	48	58.5	57.6	No mention		UN	UN
Buchler M	Yes	Yes	115	108	52	47	No mention		3.7	3.7
Chen HM	Yes	No	20	23	49	43	No mention		5.8	5.5

Author	APACHE score		Mortality rate of		Jadad score						Total dosage	Duration (hours)	Adverse effects due to Protease inhibitor administration
	Intervention	Control	Intervention	Control	Randomization	Appropriateness of randomization	Double blind	Appropriateness of double blind	Dropout	Sum			
Skyring A	UN	UN	27.5	10.7	1	0	1	0	0	2	20000-420000units	Various	No mention
Ryall RJ	UN	UN	22.2	13.3	0	0	0	0	0	0	15000-1000000units	24-240	No mention
Trapnell JE	UN	UN	15.4	8.3	1	0	1	0	0	2	115000 units	336	No mention
Baxhrach WH	UN	UN	0.0	0.0	1	1	1	0	1	4	425000 units	144	No mention
Moller G	UN	UN	2.0	4.4	0	0	0	0	0	0	500000-800000 units	Various	No mention
Baden H	UN	UN	7.1	0.5	0	0	1	0	0	1	700000 units	72	No mention
Trapnell JE	UN	UN	2.6	25.0	1	1	1	0	1	4	4200000 units	120	No mention
MRC Multicenter Trial	UN	UN	9.1	10.0	1	0	1	0	1	3	4600000 units	126	No mention
Gauthier A	UN	UN	22.0	17.4	1	0	1	0	0	2	10000000 units	120	No mention
Imrie CW	UN	UN	8.0	6.0	1	1	1	0	0	3	4500000 units	69	No mention
MRC Multicenter Trial	UN	UN	10.0	11.0	1	0	1	0	0	2	5000000 units	120	No mention
Freise J	UN	UN	16.0	4.0	1	0	1	0	0	2	8100mg	216	No mention
Yang CY	UN	UN	14.5	13.0	0	0	0	0	0	0	4200-5400mg	168-240	No mention
Goebell H	UN	UN	10.5	13.3	0	0	1	0	1	2	1800mg /day	108	No mention
Valderrama R	UN	UN	0.0	4.1	1	0	1	0	1	3	12mg/kg/day	96-240	No mention
Büchler M	UN	UN	15.2	13.5	1	1	1	1	1	5	371mg/kg	168	No mention
Chen HM	17.1	22.3	7.7	30.8	1	0	0	0	0	1	10000mg	168	No mention

Results

- 研究対象者の特性
- 研究対象とした全論文でデータは抽出可能で、研究対象者の人数、平均年齢に差はなし
- 最終包含研究は17 RCTs
  - 死亡・・・ 17研究
  - 疼痛緩和効果・・・ 2研究
  - 膵炎後仮性嚢胞形成抑制効果・・・ 5研究
  - 腹腔内膿瘍形成抑制効果・・・ 4研究
  - 手術回避の効果・・・ 3研究
  - 腸閉塞抑制効果・・・ 3研究
  - 1つ以上の合併症発生抑制効果・・・ 5研究

Results

- 研究対象者の特性
- 使用したRCTs17の背景
  - 多施設研究が11、単施設研究が6
- 出版形態
  - 16がfull paper、1つがアブストラクト
- 出版言語
  - 英語が14、ドイツ語が2、フランス語が1
- 使用薬剤
  - Aprotininが11、Gabexate Mesilateが6
  - 対照薬は全研究でPlacebo
- 具体的なアウトカム記載があったものが4、記載なしが13
- 研究サンプルサイズ記載は1RCTのみ

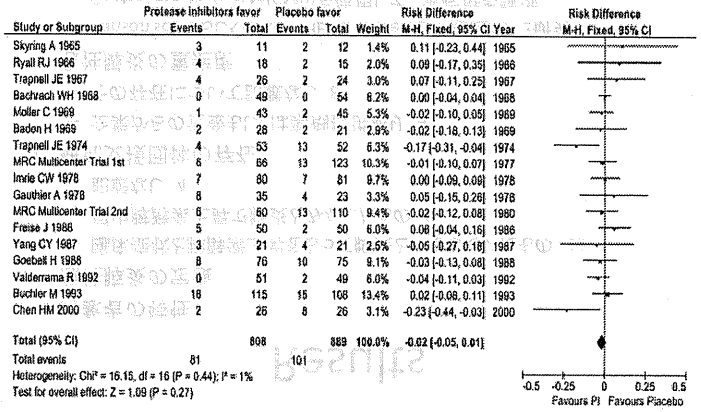
Results

- 対象者の特性
- 急性膵炎の定義
  - 臨床症状と膵酵素上昇をもって膵炎とみなしていたもの 11
  - 尿中膵酵素上昇で膵炎とみなしたもの 2
  - 記載なし 4
- 研究支援団体の存在
  - 企業からの資金もしくは薬剤提供あり 9
  - その存在について記載なし 8
- 急性膵炎の重症度
  - Ranson scoreもしくはAPACHE-Ⅱ scoreとして定量化 2研究
  - Control mortality rate(CMR)を使用して、重症度を評価
    - 対照群で10%以上の死亡率は10研究存在
- いずれの研究も有害事象の記述自体なし

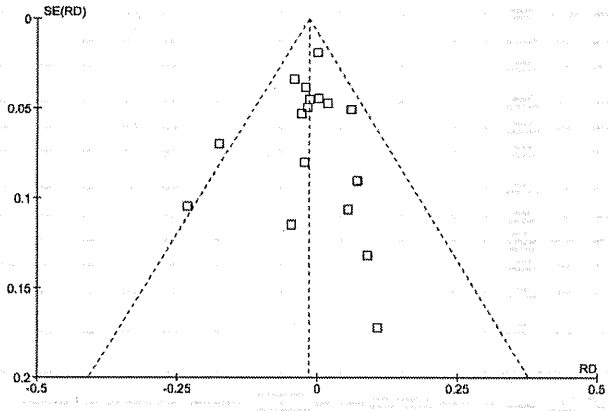
Results

- Quality assessment
- 全平均 Jadad score 2.1
  - –range 0-5
  - –0点研究を除いた平均 2.6
- High quality (Jadad score>3 points)
  - –6 studies
  - –それらの平均 3.7

Results(Overall mortality)



Results



Results

Death	pooled Risk Difference	95%CI lower	95%CI upper	NNT	95%CI lower	95%CI upper
Overall	-0.02	-0.05	0.01	74.4	23.3	infinite
Aprotinin	-0.01	-0.05	0.02			
Gabexate Mesilate	-0.02	-0.07	0.03			
With sponsor	-0.01	-0.05	0.02			
Withou sponsor	-0.02	-0.06	0.03			
CMR>10%	-0.03	-0.07	0.01			
CMR>20%	-0.19	-0.31	-0.08			
CMR>30%	-0.23	-0.27	-0.19			
Jadad>3	-0.02	-0.06	0.01			
Abdominal pain	-0.26	-0.4	-0.13	3.9	2.5	10.1
Jadad>3	-0.14	-0.32	0.03			
Pseudocysts	0	-0.04	0.04	57.3	20.2	infinite
Intra-abdominal abscess	-0.01	-0.04	0.01	113.1	39.7	infinite
Surgical intervention	-0.08	-0.16	-0.01	11.8	6.1	493
Jadad>3	0	-0.03	0.04			
Bowel obstruction	-0.06	-0.12	-0.01	6.3	4	14.8
Jadad>3	-0.03	-0.07	0.01			
Any complications	-0.01	-0.08	0.06	76.4	11.2	infinite

Discussion

- 前回のメタ分析との相違点
- 中等度から重症膵炎に対するタンパク分解酵素阻害剤の効果
  - –CMR>10%　では効果確認できず
  - –CMR>20%　では効果が有意
- 重症症例の研究は全体として質が低い
  - – CMR>20%のRCTの平均 Jadad score 2.5点、
  - – CMR>30%では1点
- 重症例では効果の過大評価の可能性がある

Discussion

- バイアスの存在について
  - – 企業からの資金もしくは薬剤提供あり 9
  - – その存在について記載なし 8
- 提供ありのRCT
  - – いずれもタンパク分解酵素阻害剤製造のメーカーからで、資金提供が1、薬剤提供が9（重複あり）
- グラントの存在の記載がなかったRCTs 8
  - – これらはすべて「資金提供や薬剤提供なし」の記載ではなく、資金もしくは薬剤提供の有無が不明

Discussion

- 各種バイアスの影響
- 主要アウトカムやサンプルサイズ計算の記載
  - – 主要アウトカムの明記・・・4
  - – サンプルサイズ計算・・・1
- すべての研究でタンパク分解酵素阻害剤投与による有害事象について記述自体無し。
  - –「有害事象は無し」と記述されていない
  - – 厳密に言えば、安全性は判断できない。

Discussion

- 主要アウトカムやサンプルサイズの記載はCONSORT声明で明示化され、その後報告の質が改善傾向
  - – Begg C,et al. JAMA 1996.
  - – Plint AC, et al. Med J Aust 2006.
  - – Hopewell S, et al. BMJ 2010.
- 日本発98RCTs（2004発表）で、主要・副次アウトカムは26%、サンプルサイズ計算は23%のみで記載あり
  - – Uetani K, Nakayama T, et al. Inter Med 2009.
- 今回の17RCTsの多くで、多数のアウトカムから都合のよい結果を研究者が選択し、それを提示している可能性も否定できない（アウトカム報告バイアス）
  - – Chan AW, et al. JAMA. 2004

Discussion

- 研究の限界
  - 一般的に受け入れられている重症度でサブグループ解析が不十分
    - 17RCTsのうち、重症度を定量的に示していたのは2つのみ
    - 中等度から重症膵炎としてCMR>0.10を代用
  - CMRはretrospective index であり、膵炎重症度の客観的指標として妥当性に疑問
  - APACHE-Ⅱなどで重症度判定されたRCTの実施と、それらを統合したメタ分析が望まれる。

Conclusion （暫定）

- タンパク分解酵素阻害薬に急性膵炎の明確な死亡抑制効果は認められなかった
- 中等度から重症膵炎ではやや死亡を抑制する可能性が見られたが、質の低い少数の報告によるものであった。
- 死亡以外のアウトカムでもタンパク分解酵素阻害薬の効果は明らかではなかった。

個々のエビデンス（論文）に関して

- **Limitations (risk of bias)**

1. 適正な割り付け順序の作成
2. 割り付けのコンシールメント
3. 盲検化
4. 不完全なアウトカムデータの対処
5. アウトカム報告バイアスの有無
6. その他のバイアス

– (Cochrane collaboration)

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個々のエビデンスの質評価

Author	Year	適切な割り付け順序の作成	割り付けのconcealment	盲検化	不完全なアウトカムデータの対処	アウトカム報告バイアスの有無	ITT analysis
Skyring A	1965	no	yes	yes	no	no	no
Ryall RJ	1966	no	no	no	no	no	no
Trapnell JE	1967	no	yes	yes	no	no	no
Bachrach WH	1968	no	yes	yes	no	no	no
Moller C	1969	no	no	no	no	no	no
Baden H	1969	no	yes	yes	no	no	no
Trapnell JE	1974	no	yes	yes	no	no	no
MRC Multicenter Trial	1977	no	yes	yes	no	no	no
Gauthier A	1978	no	yes	yes	no	yes	no
Imrie CW	1978	no	yes	yes	no	no	no
MRC Multicenter Trial	1980	no	yes	yes	no	yes	no
Freise J	1986	no	yes	yes	no	no	no
Yang CY	1987	no	no	no	no	no	no
Goebell H	1988	no	yes	yes	yes	no	no
Valderrama R	1992	yes	yes	yes	yes	no	no
Buchler M	1993	yes	yes	yes	yes	yes	yes
Chen HM	2000	no	no	no	no	yes	no

エビデンス（総体）の質

- 高・・・今後の研究によって効果推定値に対する確信が変わる可能性は低い。
- 中・・・今後の研究によって効果推定値に対する確信に重要な影響がおよぶ可能性が高く、推定値が変わる可能性がある。
- 低・・・今後の研究によって効果推定値に対する確信に重要な影響がおよぶ可能性が非常に高く、推定値が変わる可能性が高い。
- 非常に低・・・あらゆる効果推定値が不確実。

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GRADE システムによるEvidenceの”質”評価

Study design	Rate-Down	Rate-Up	Quality		
複数のランダム化比較試験= 高 （変更後＝中） 複数の良質な観察研究= 低	①限界 (-1, -2) ②結果の非一貫性 (-1, -2) ③PICOの非直接性 (-1, -2) ④結果が不精確 (-1, -2) ⑤出版バイアス (-1, -2)	①関連性（効果の大きさ）(+1, +2) ②交絡因子のために効果が減少 (+1) ③用量反応勾配 (+1)	High moderate Low	A B C	⊕⊕⊕⊕ ⊕⊕⊕○ ⊕⊕○○
その他の研究やエキスパート意見 = 非常に低	原則として、グレードは上げない		very low	D	⊕○○○

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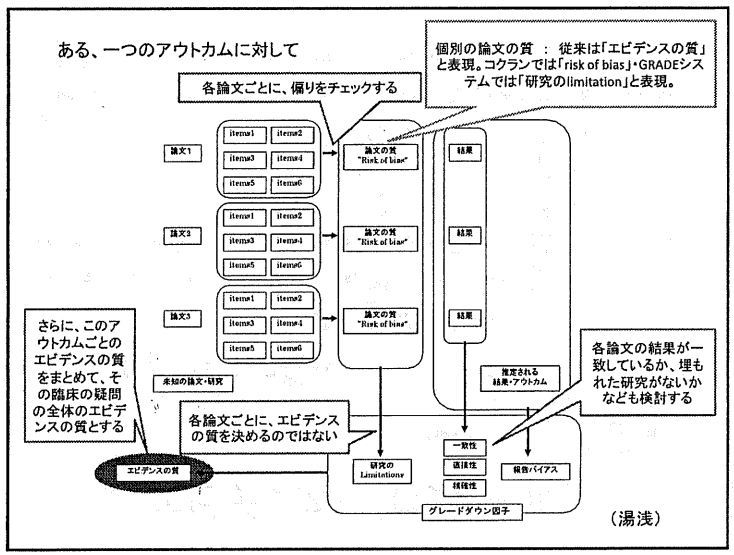
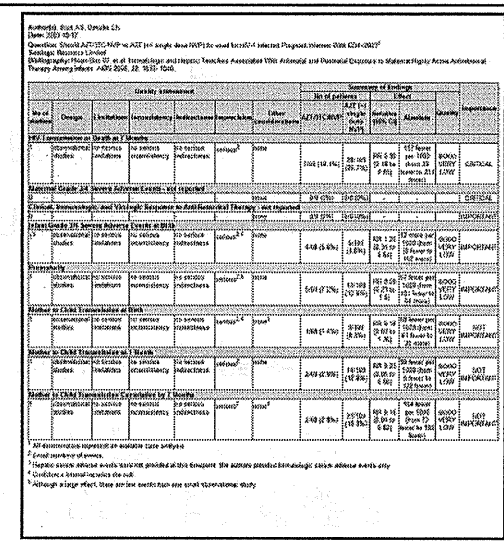


GRADE evidence profile



エビデンス・プロフィール

質の評価										結果の要約							アウトカムの重要性	square(%)
アウトカム	研究数	研究デザイン	限界	非一貫性	非直接性	不精確さ	報告バイアス	患者数 介入 対象者数	患者数 介入 イベント数	対照 イベント割合	対照 対象者数	対照 イベント数	対照 イベント割合	効果 リスク差	95%CI	質		
1. 死亡抑制	17	RCTs	-2	-2	-1	-1	-1	808	81	10.0%	889	101	11.4%	-0.02%	-0.05, 0.01	中-低	critical	1
2. 疼痛抑制	2	RCTs	-2	-1	-2	-2	-2	75	24	32.0%	80	46	57.5%	-0.26%	-0.40, -0.13	低	important	85
3. 仮性嚢胞形成抑制	5	RCTs	-2	-1	-2	-2	-2	238	13	5.5%	276	16	5.8%	0.00%	-0.05, 0.04	中-低	important	0
4. 膿瘍形成抑制	4	RCTs	-2	-1	-2	-1	-2	212	3	1.4%	261	6	2.3%	-0.01%	-0.04, 0.01	中-低	important	0
5. 手術回避	3	RCTs	-2	-2	-2	-2	-2	217	46	21.2%	209	62	29.7%	-0.08%	-0.16, -0.00	低	important	60
6. イレウス予防	3	RCTs	-2	-2	-2	-2	-2	201	66	32.8%	244	119	48.8%	0.00%	-0.12, 0.00	低	important	59
7. その他何らかの合併症抑制	5	RCTs	-2	-1	-2	-2	-2	302	101	33.4%	282	98	34.8%	-0.01%	-0.08, 0.06	中-低	important	0

GRADEによる推奨度 :考慮する要因

- 重大なアウトカムに関するエビデンスの質
- 利益と不利益のバランス
- 患者の価値観や好み
- コストや資源の利用

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副作用・安全性:日本語論文

医学中央雑誌 検索式
#1 タンパク分解酵素阻害薬 #2 副作用 #3 合併症 #4 安全性
#5 急性膵炎 #1 AND (#2 OR #3 OR #4) AND #5

症例報告を除き、解説、総説で51件ヒット。
そのうち通読可能かつ副作用情報の記載あるものは1つのみ。

荒田慎寿、森脇義弘、杉山貢. 特集 急性膵炎 今日の臨床的諸問題 重症化阻止はいかに 抗菌薬、抗酵素剤の使い方と補液療法. 肝胆膵 2005;51:1091-1102.

Gabexate Mesilate
急性膵炎に対して100-300mg/dayを基本投与量とし、600mg/dayまで増量可。投与期間の明確な基準はない。
副作用はショック、アナフィラキシーショック、アナフィラキシー様症状。過敏症のある症例は禁忌。全体の副作用は2.18%で、主なものに血管痛、静脈炎、発疹、血圧低下、嘔吐など(出典不明)。

Ulinastatin
急性膵炎には25000-50000万単位を使用。150000単位/日まで使用可。原則投与期間は3日。副作用にショック。過敏症のある症例は禁忌。全体の副作用は0.8%に見られ、肝酵素上昇、白血球減少、発疹、掻痒、消化器症状、血管痛など(出典不明)。

コスト

	標準的使用方法	単価【円】	副作用 TOP 5	副作用 頻度	観察総症例数	出現総数
ミラクリッド (Ulinastatin)	1回 2.5-5万単位 1日 1-3回	1063 (2.5万単位)	AST、ALT上昇 白血球減少 発疹 下痢 血管痛	0.4% 0.2% 0.1% 0.1% 0.1%	8710	74
FOY (Gabexate mesilate)	20-30mg/kg/day	3641 (500mg)	血管痛 発疹 AST、ALT上昇	1.9% 0.3% 0.3%	1952	56
トラジロール (Aprotinin)	25-100万単位/日	920 (5万単位)	発疹 血管痛 AST、ALT上昇	0.1% 0.1% 0.1%	不明	不明
フサン (Nafamostat mesilate)	1回 10mg 1日 1-2回	1217 (10mg)	AST、ALT上昇 発疹 高K血症	0.8% 0.3% 0.2%	6732	117

出典 各添付文書

Delphi法

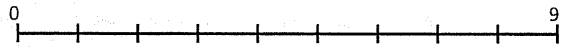
1. クリニカルクエスチョンに基づき，重要なcueをいくつか含む臨床的シナリオを準備する
2. シナリオの症例に対して，可能性のある選択肢を列挙する（グループとは別に行っても良い）
3. グループメンバーに，各選択肢への同意の程度を評点づけてもらうアンケートを送付
   - 「全く同意できない」を0，「完全に同意する」を9とする
1. 前回のアンケートの集計結果を連絡し，再度アンケートを行う
2. 点数を集計し，全体の合意の程度を検討する．ある程度のコンセンサスが得られれば終了，まだコンセンサスが得られていなければ4を繰り返す

特徴：議論がない

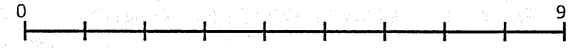
アンケート用紙：1回目

シナリオの患者（合併症のない急性上気道炎）に対する治療法として，次の各選択肢にどの程度同意されますか？

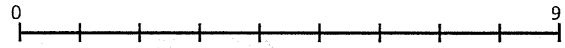
a. （合併症の発症を減らすとのエビデンスはないが，特に害はないと考えられる）水分の摂取を勧める



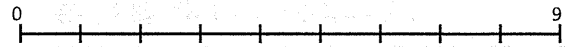
b. （症状が半日早く消失するとのエビデンスがある）抗生剤を投与する



c. （発熱や咽頭痛症状を軽減するとのエビデンスがあるが，治療までの期間を延長させるとのエビデンスがある）消炎鎮痛剤を処方する

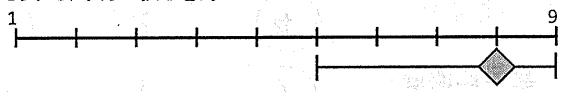


d. 何もしない

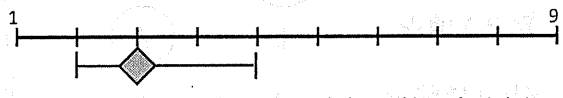


アンケート用紙：2回目以降

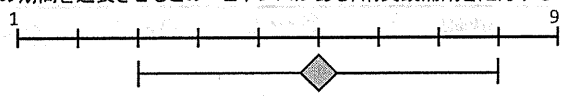
a. （合併症の発症を減らすとのエビデンスはないが，特に害はないと考えられる）水分の摂取を勧める



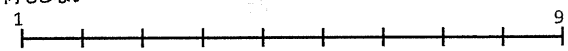
b. （症状が半日早く消失するとのエビデンスがある）抗生剤を投与する



c. （発熱や咽頭痛症状を軽減するとのエビデンスがあるが，治療までの期間を延長させるとのエビデンスがある）消炎鎮痛剤を処方する



d. 何もしない



RANDバージョンのNGT

- メンバーは9名
- 1（著しく不適切）～9（極めて適切）までの9ポイント評価（5は利益と害がほぼ同等）
- 最初の評点はディスカッション前に個別に実施
- 評価の結果がディスカッションに提示される
- 議論の後，再評点
- 1-3，4-6，7-9の何れかに7名が入れば合意とみなし，また3名以上が入れた段階が2つ以上あれば合意なしとする