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3-35 溶血性レンサ球菌感染症（含む TSLS）

■特 徴

(1) グラム陽性球菌として代表的なレンサ球菌 *Streptococcus* 属は，羊血液寒天培地における溶血性に基づいて完全溶血（β型，血液平板上のコロニー周辺が透明）・部分溶血（α型，赤血球が部分的に消化されコロニー周辺が緑色）・非溶血（γ型，全く溶血なし）に分けられる．さらに，細胞壁におけるC多糖体の抗原性に基づくLancefieldによる分類では，A～V（IとJは欠番）に群別され，主にラテックス凝集反応を用いて判定される．

(2) ヒトに病原性を示す主なβ溶血性レンサ球菌として，A群レンサ球菌GASである *Streptococcus pyogenes*・B群レンサ球菌GBSである *S.agalactiae*・主にG群/C群レンサ球菌GGS/GCSに属する *S.dysgalactiae* subsp. *equisimilis*：SDSEや *S.anginosus* groupとして総括される *S.anginosus/S.constellatus/S.intermedius* といった菌種が挙げられる[1]（表1），SDSEは平板上で大きなコロニーを呈するのに対して，*S.anginosus* groupによるコロニーは小さいため鑑別できる[1]（表1）．

(3) 全ゲノム解析のデータを病原因子の点から検討すると，GAS＞SDSE＞GBSの順にその病原性の強さが想定される．

(4) 疫学解析の分子マーカーとして，GASとSDSEでは菌表層に存在するMタンパク（コードしている遺伝子はemm）先端（N末端側）の超可変領域における塩基配列の多様性によって *emm* 型が適用される．GBSはその表面にある莢膜を構成する糖の組合せにより，

表1　各種β溶血性レンサ球菌における主な性状[1]

Species	Lancefield group	Hemolysis type	Colony size	Hosts	BA	PYR	CAMP	VP	β-GLU	β-GAL
S. pyogenes	A	β	Large	Humans	+	+	−	−	−	v
S. agalactiae	B	β	Large	Humans, cows	−	−	+	−	v	−
S. dysgalactiae subsp. *equisimilis*	A, C, G	β	Large	Humans	−	−	−	−	+	−
S. dysgalactiae subsp. *dysgalactiae*	C, L	none, α, (β)	Large	Animals (pigs, cows)	−	−	−	−	+	−
S. equi subsp. *equi*	C	β	Large	Horses	−	−	−	−	+	−
S. equi subsp. *zooepidemicus*	C	β	Large	Animals (horses, pigs), humans	−	−	−	−	+	−
S. canis	G	β	Large	Animals (cows, dogs, cats)	−	−	+	−	v	−
S. anginosus group[a]	A, C, G, F, none	β, α, none	Small	Humans	−	−	−	+	−	−

BA, Bacitracin ; PYR, pyrrolidonyl-arylamidase test ; CAMP factor reaction (synergistic hemolysis in presence of *S. aureus* β-hemolysin) ; VP, Voges-Proskauer test ; β-GUR, β-D-glucuronidase test ; β-GAR, β-galactosidase test　+, positive ; −, negative ; v, variable

莢膜血清型として現在10種類（Ⅰa，Ⅰb，Ⅱ，Ⅲ，Ⅳ，Ⅴ，Ⅵ，Ⅶ，Ⅷ，Ⅸ）に分類される．

(5) 溶血性レンサ球菌感染症は，侵襲性感染症（血液・髄液・関節液・胸腹水等の無菌的検体より菌が分離同定）と非侵襲性の局所感染症（たとえば，咽頭炎／扁桃炎・伝染性膿痂疹）に分けられる．

(6) 侵襲性感染症における重症型として劇症型溶血性レンサ球菌感染症（レンサ球菌性毒素性ショック症候群，toxic shock-like syndrome：TSLS）がある．TSLSの症例定義を表2に示す．TSLSを除く侵襲性感染症には，

①肺　炎

②皮膚軟部組織感染症（丹毒／蜂窩織炎／壊死性筋膜炎）

③尿路感染症 urosepsis

④化膿性関節炎・骨髄炎・感染性心内膜炎・髄膜炎・深部膿瘍

などが含まれる．

(7) 年齢別の分布ではSDSEやGBSによる侵襲性感染症は基礎疾患を有する高齢者において顕著であり，GBSによる新生児髄膜炎・敗

表 2　レンサ球菌性毒素性ショック症候群（TSLS）の症例定義

I．レンサ球菌が以下の部位より検出されること a. 平素無菌的である部位：血液，髄液，胸水，組織生検材料など b. 無菌的でない部位：咽頭，喀痰，膣，皮膚表層の病変など
II．重篤な臨床所見．特に以下のaとbが同時に認められること a. 低血圧（収縮期血圧＜90 mmHg） b. 以下の所見が少なくとも二つ以上認められること 1. 腎機能の低下（血清クレアチニン値＞2 mg/dL） 2. 血液凝固障害：血小板数 10 万/μL 以下または播種性血管内凝固（DIC） 3. 肝機能異常（AST/ALT/総ビリルビン値が正常上限値の 2 倍以上） 4. 成人呼吸窮迫症候群（ARDS） 5. 全身皮膚の紅斑様皮疹・落屑を含む 6. 軟部組織壊死（壊死性筋膜炎・筋炎・壊疽を含む） 7. 中枢神経症状（他に原因のない痙攣・意識消失など）

Ia＋II→確定診断
Ib＋II→他に原因となる疾患が認められない場合，本疾患を疑う．

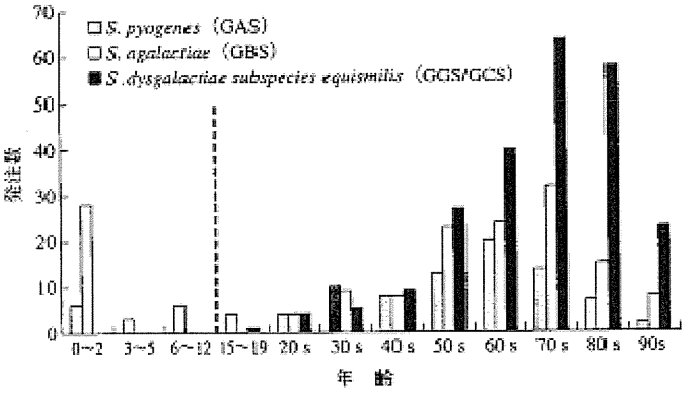

図 1　侵襲性レンサ球菌感染症の年齢分布[2]
侵襲性 G 群/C 群レンサ球菌感染症は 70～80 歳代に発症することが多く，
B 群レンサ球菌感染症は 4 ヶ月以下と 70 歳代に発症のピークがある．
GAS：A 群レンサ球菌
GBS：B 群レンサ球菌
GGS/GCS：G 群/C 群レンサ球菌

血症も見られる[2]（図 1）．

(8) GAS や SDSE による侵襲性感染症由来株で最も多い型である *emm1* や *stG6792* は，同疾患による予後不良（死亡や後遺症残存）との関連性が報告されている[2]．侵襲性 GBS 感染症においては，小児で

はⅢ型が顕著（髄膜炎の77%を占める）で，成人ではⅠb型とⅤ型が多くみられる．

(9) GASの発赤毒素による小児に特有な病態として猩紅熱があり，GAS感染症に罹患した後，数週間してから発症するリウマチ熱や急性糸球体腎炎のような病態もある．

■ 感染経路

(1) レンサ球菌が定着する部位として，
①上気道（咽頭扁桃・口腔）
②皮　膚
③泌尿生殖器
④腸　管
が推定される．このような部位が粘膜障害や皮膚バリアの破綻（創傷）を契機として宿主への侵入門戸（内因性）となりうるが，臨床上，侵入門戸が不明な症例もある．

(2) 汚染された飲食物からの経口感染（外因性）もある．上気道に定着している場合は，飛沫経路を介して他者へ伝播（外因性）される．

■ 接触感染

皮膚・泌尿生殖器・腸管に定着している場合は，浸出液や排泄物に対する直接あるいは間接の接触経路を介して他者へ伝播（外因性）される．

■ 潜伏期間

1～3日．

■ 症　状

(1) 侵襲性感染症であれば，初感染巣（下気道・皮膚軟部組織等）や播種性病巣（関節・骨髄・髄膜等）毎に症状が異なる．ただし，urosepsisの場合や高齢者での発症では症状に乏しいので注意が必要である[3]．

(2) 非侵襲性である咽頭炎/扁桃炎では高熱とともに咽頭痛，伝染性膿痂疹は皮膚症状を呈する．

↑p07

■ 治療法

(1) TSLS ではペニシリン G（2,400 万単位/日，分 6 で静注）＋クリンダマイシン（900 mg を 8 時間毎に静注）を投与する．壊死性筋膜炎に対する壊死組織の切除や循環動態維持といった全身管理が必要である．

(2) 丹毒/蜂窩織炎に対してはペニシリン G（100～200 万単位を 6 時間毎に静注）を投与する．

(3) 咽頭炎/扁桃炎ではセフロキシムアキセチル（成人で 250 mg を 1 日 2 回 4 日間，小児で 20 mg/kg/日・分 2 を 4～10 日間）を内服する．

■ 予防法

(1) 新生児 GBS 感染症の予防として，妊婦（35～37 週）に対する膣および直腸の擦過培養の結果に基づいて，出産にて入院した時点から予防的に抗菌薬を投与（ペニシリン G を初回 500 万単位静注し，以降分娩まで 4 時間毎に 250 万単位静注）する．

(2) M タンパクを標的抗原とした GAS ワクチンの臨床試験が展開されているが，市場には流通していない．

(3) うがいや手洗いは励行するが，菌に対する特別な消毒は必要ない．

■ 感染症法による取扱い

劇症型溶血性レンサ球菌感染症は，5 類感染症のうちの全数把握感染症として医師は診断後 7 日以内に都道府県知事等へ報告する．A 群溶血性レンサ球菌咽頭炎は，5 類感染症のうちの小児科定点把握感染症として週単位で翌週の月曜日に届け出なければならない．細菌性髄膜炎であれば，5 類感染症のうちの基幹定点把握感染症として週単位で翌週の月曜日に届け出を行う．

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3-3 ライム病

■特　徴

ライム病 Lyme disease（または Lyme borreliosis）はノネズミやシカ，野鳥などを保菌動物とし，マダニ科マダニ属 *Ixodes ricinus* 群のマダニによって媒介される．スピロヘータの一種，ボレリア Borrelia による感染症である．野生動物では感染しても発症しないが，ヒト，犬，馬，牛では臨床症状を示す．アメリカコネチカット州のオールドライム Old Lyme で最初に確認されたためライム病と呼ばれるようになった．

ボレリアを媒介する *Ixodes ricinus* 群のマダニは北半球の温帯から亜寒帯に広く分布している．ユーラシア大陸では *Ixodes ricinus* とシュルツェマダニ *Ixodes persulcatus* が，北アメリカ大陸では *Ixodes scapularis* と *Ixodes pacificus* が *Borrelia burgdorferi* を消化管に保菌している．日本では *Ixodes persulcatus* が媒介者となっている．*Ixodes persulcatus* は，日本では中部地方以北で多いといわれており，北海道などでは平地でもみられる．

病原体であるボレリアは，全長約 10 μm，直径 0.2～0.3 μm の螺旋（らせん）状のスピロヘータであり，現在までに 10 種に分類されている．本疾患の原因となるのは広義の *Borrelia burgdorferi* であり，具体的には *Borrelia burgdorferi* sensu stricto，*B. garinii*，*B. afzelii* がヒトに病原性を示すことが確認されている．わが国では *B. garinii*，*B. afzelii* が主な病原体となっている．北米では *Borrelia burgdorferi*，欧州では *B. burgdorferi* と *B. garinii*，*B. afzelii* が主な病原体となっている．

夏から初秋にかけて，樹木の多い地域に発生する．欧米では年間数万人のライム病患者が発生している．わが国では，1986 年に初のライム病患者が報告された．それ以降，主に本州中部以北で発見されており，標高 800 m 以上の山岳地域などで発生がみられる．これまでは特に北海道および長野県からの報告が多い．ただし，欧米からの輸入症例が増加

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COMMISSION REPORT

Survey on geriatricians' experiences of adverse drug reactions caused by potentially inappropriate medications: Commission report of the Japan Geriatrics Society

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Aim: The Japan Geriatrics Society (JGS) developed the guidelines for medical treatment and its safety in the elderly and the list of potentially inappropriate medication use, a Japanese version of the Beers list, in 2005. The JGS working group in collaboration with the Japan Broadcasting Corporation conducted the survey to geriatricians to investigate their experiences of adverse drug reactions (ADR) caused by potentially inappropriate medications.

Methods: In September 2008, the survey mails were sent to all the JGS certified geriatricians ($n = 1492$). The questionnaire consisted of 1 year of experiences of ADR of any type, past experiences of ADR by the use of antipsychotic benzamides, hypnotic benzodiazepines, digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and additional drugs, and their attitudes to reduce the dose/number of drugs for the prevention of ADR.

Results: A total of 425 geriatricians responded (response rate 29%). Seventy-two percent experienced ADR within 1 year. Past experiences of ADR were reported by 79% for antipsychotic benzamides, 86% for hypnotic benzodiazepines, 70% for digoxin and 37% for vitamin D_3. Free responses included frequent ADR by non-steroidal anti-inflammatory, antihypertensive, antiplatelet, anti-arrhythmic, antidiabetic and antidepressant drugs. Reduction of drugs for ADR prevention was attempted by 93%.

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Conclusion: This survey showed that most geriatricians experience ADR and take preventive measures for ADR. The results can be used for education and the development of new guidelines. **Geriatr Gerontol Int 2011; 11: 3–7.**

Keywords: adverse drug reactions, Beers list, geriatrician, polypharmacy, side-effect.

Introduction

Adverse drug reactions (ADR) are more frequent and severe in the elderly than in young adults. A recent systematic review[1] of prospective observational studies reported that 10.7% of hospital admissions were associated with ADR in elderly patients, while 6.3% were so in young adults. Surveys performed in acute care hospitals in Japan also showed that inpatients aged 70 years or older were 1.5-fold more likely to develop ADR than those under 60 years of age,[2] and that the ADR incidence among elderly inpatients was 6–15%.[3] It has been reported from Western countries that ADR occur in more than 10% of outpatients or nursing home residents.[4]

Although many factors relate to the high ADR incidence in the elderly, overdoses resulting from age-related changes of pharmacokinetics/pharmacodynamics and polypharmacy may be of critical importance.[2–4] Because the evidence for the elderly is limited, practical guidelines to medical treatment and its safety are required in the field of geriatric medicine.

The Japan Geriatrics Society (JGS) has conducted educational activities through scientific sessions and official journals to reduce ADR. As part of activities, the ad hoc committee "Working group on guidelines for medical treatment and its safety in the elderly" was set up in 2003, and the JGS guidelines for medical treatment and its safety in the elderly were published in 2005.[5] In the guidelines, the list of medications that should be prescribed with special attention to elderly patients was reported and was put on the JGS website. This list, a Japanese version of the Beers list,[6,7] consists of 45 drugs or drug classes that may be harmful or less efficient, thus potentially inappropriate for elderly patients, and can be applied to reduce ADR and polypharmacy in clinical settings of geriatric medicine and nursing-care facilities.[5]

Although the mass media expressed an interest in these activities, the JGS should increasingly accumulate the evidence and make a proposal on pharmacotherapy of the elderly for public education. For this purpose, the JGS working group in collaboration with the Japan Broadcasting Corporation (NHK) conducted the survey to JGS certified geriatricians to investigate their experiences of ADR caused by potentially inappropriate medications. This commission report of the working group shows the survey results.

Methods

Mailing and collection of the questionnaire

In September 2008, the questionnaire was mailed by the NHK to all the JGS certified geriatricians (n = 1492) who appeared on the JGS website. In the cover letter, a brief introduction including the background and aim of the survey was described, followed by the statement that this survey was carried out in collaboration with the NHK and the JGS working group. The JGS version of the Beers list (Table 1 and detailed explanation) was included in the mail for options of additional drugs. The responder was asked to return the questionnaire to the NHK by fax without his/her name.

Questionnaire item

The questionnaire consisted of 1-year experiences of ADR of any type (yes/no question), past experiences (frequent, occasional or none) of ADR by the use of antipsychotic benzamides (sulpiride, sultopride), hypnotic benzodiazepines (flurazepam, haloxazolam, quazepam, triaxolam), digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and free additions, and their attitudes to reduce the dose/number of drugs for the prevention of ADR (yes/no question). In addition, free comments on the problems and approaches related to pharmacotherapy in the elderly were asked. The above four classes of drugs were chosen from the JGS version of the Beers list (Table 1) because these drugs were considered frequently prescribed to elderly patients.

Statistical analysis

The data are shown as the number and the percent of subjects. The χ^2-test was performed to analyze the associations between ADR experiences.

Results

A total of 425 geriatricians responded, resulting in a response rate of 28.5%. The response rate would have been 29.1% if the 30 subjects to whom the mails were not successfully delivered were excluded.

The summary of the results is shown in Table 2. Seventy percent of the geriatricians reported

Table 1 List of medications that should be prescribed with special attention to elderly patients (JGS version of the Beers list)

Class	Drug (generic name)
Antihypertensive (central sympathetic blocking agents)	Methyldopa
	Clonidine
Antihypertensive (rauwolfia)	Reserpine
Antihypertensive (short-acting calcium channel blockers)	Nifedipine
Vasodilator	Isoxsuprine
Cardiac glycoside	Digoxin (≥0.15 mg/day)
Anti-arrhythmic	Disopyramide
	Amiodarone
Antiplatelet	Ticlopidine
Hypnotic (barbiturates)	Pentobarbital
	Amobarbital
	Barbital
	Chlorpromazine, promethazine, phenobarbital
Hypnotic (benzodiazepines)	Flurazepam
	Haloxazolam
	Quazepam
	Triaxolam
Anxiolytic (benzodiazepines)	Chlordiazepoxide, diazepam
Antidepressants	Tricyclic (amitriptyline, imipramine, clomipramine)
	Maprotiline
Antipsychotic (phenothiazines)	Thioridazine, chlorpromazine, levomepromazine
Antipsychotic (butyrophenones)	Haloperidol, timiperone, bromperidol
Antipsychotic (benzamides)	Sulpride, sultopride
Anti-parkinsonian	Trihexyphenidyl
Antiepileptic	Phenobarbital
	Phenytoin
Narcotic analgesic	Pentazocine
Non-steroidal anti-inflammatory	Indometacin
	Diclofenac sodium, naproxen, piroxicam
Irritant laxative	Caster oil
Skeletal muscle relaxant	Methocarbamol
Soothing muscle relaxant	Oxybutynin
Intestinal antispasmodic	Butylscopolamine
	Propantheline
Anti-emetic	Metoclopramide
	Domperidone
Androgen	Methyltestosterone
Estrogen	Estrogens
Thyroid hormone	Dried thyroid
Hypoglycemics (1st-generation sulfonyl urea)	Chlorpropamide
	Acetohexamide
Hypoglycemics (biguanides)	Metformin
	Buformine
Iron	Fe (≥300 mg/day)
Vitamin D	Alfacalcidol (≥1.0 μg/day)

Doses in the parentheses are applicable for digoxin, Fe and alfacalcidol. This list with detailed explanation such as trade names and alternative drugs was enclosed in the questionnaire.

experiences of ADR within a year, even though non-responders ($n = 7$) were included in those without experience. Regarding past experiences of ADR, approximately a quarter of the geriatricians reported frequent ADR experiences by antipsychotic benzamides and hypnotic benzodiazepines. Seventy to eighty percent frequently or occasionally experienced ADR by these two classes of drugs and by digoxin, and

Table 2 Geriatricians' experiences of adverse drug reactions (ADR) and their attitudes to reduce drugs for the prevention of ADR ($n = 425$)

1. One-year experiences of ADR of any type ($n = 418$)			71.5%
2. Past experiences of ADR by use of the following drugs			
	Frequent	Occasional	Frequent + Occasional
(i) Antipsychotic benzamides ($n = 381$) (sulpiride, sultopride)	93 (24.4%)	207 (54.3%)	300 (78.7%)
(ii) Hypnotic benzodiazepines ($n = 386$) (flurazepam, haloxazolam, quazepam, triaxolam)	93 (24.1%)	241 (62.4%)	334 (86.5%)
(iii) Digoxin (≥0.15 mg/day) ($n = 382$)	33 8.6%)	234 61.3%)	267 69.9%)
(iv) Vitamin D_3 ($n = 373$) (alfacalcidol ≥1.0 μg/day)	14 (3.7%)	125 (33.5%)	139 (37.3%)
3. Past experiences of ADR (free responses; $n = 240$)			
Class of drugs	Frequent	Occasional	Frequent + Occasional
(i) Non-steroidal anti-inflammatory	60	34	94
(ii) Antihypertensive	19	27	46
(iii) Antiplatelet	17	21	38
(iv) Antidiabetic	19	15	34
(v) Anti-arrhythmic	13	17	30
(vi) Antidepressant	15	10	25
(vii) Anti-Parkinson	9	12	21
(viii) Warfarin	6	7	13
4. Reduction of the dose/number of drugs for the prevention of ADR ($n = 417$)			93.0%

Data in the parentheses indicate the number of responses to each questionnaire item. Each value indicates the number of cases and the percentage. Free responses to past experiences of ADR show the classes of drugs with more than 10 cases.

nearly 40% by vitamin D_3. Interestingly, the χ-square test showed that 1-year experiences of ADR of any type were significantly associated with ADR experiences by each of the four classes of drugs (data not shown), suggesting that some geriatricians frequently experience ADR of various types, and others do not. Free responses ($n = 240$) included common ADR by non-steroidal anti-inflammatory drugs; 25% of the responders reported frequent ADR and 39% reported frequent or occasional ADR. More than 90% of the geriatricians reported that they reduced the dose and number of drugs for the prevention of ADR.

Free comments on the problems and approaches related to pharmacotherapy in the elderly were summarized as follows: (i) lack of understanding about drug metabolism and ADR by doctors and patients, and need for their education; (ii) training of geriatricians who understand medical treatment in the elderly and are able to align prescriptions in a comprehensive manner; (iii) medication errors and a lack of prescription information derived from multi-consultations are problematic, thus a medication management and interdisciplinary collaboration system must be established; and (iv) because a medical fee system in which an easy medication is profitable rather than attentive listening may cause polypharmacy, guidelines and a new medical system to block this pathway should be created.

Discussion

In this questionnaire survey, although the mails were sent from the NHK, approximately 30% of the JGS certified geriatricians responded, expressing their high interest in medical treatment in the elderly. Seventy percent of them reported ADR experiences within a year, while more than 90% attempted to reduce the dose and number of drugs for the prevention of ADR.

Although most geriatricians reported ADR experiences, the prevalence should be carefully interpreted. First, sampling bias and overestimation are possible, because geriatricians who experienced more ADR and were conscious of ADR might have responded more actively. Second, there is a problem in reliability of ADR, because judgments of ADR including causality and severity may vary between geriatricians, and ADR experiences were dependent on memory rather than records. The questionnaire item concerning the frequency of ADR for individual drugs was also ambiguous. Because the frequency of ADR is related to the frequency of prescriptions, free responses included many common medications for elderly patients, such as non-steroidal anti-inflammatory drugs and antihypertensive drugs.

As described above, this survey was not designed to determine the incidence of ADR per patient or drug. The aim was to accumulate the opinions of JGS certified

geriatricians about ADR and pharmacotherapy, thus the results may have reflected their awareness of the issues. Taken together, it is reasonable that antipsychotic benzamides, hypnotic benzodiazepines and digoxin (≥0.15 mg/day) are included in the JGS version of the Beers list, because 70–80% of geriatricians reported ADR experiences by these drugs. This questionnaire also asked about ADR by vitamin D, which was not included in the lists of potentially inappropriate medications in Western countries.[6–8] Vitamin D_3 (alfacalcidol ≥1.0 μg/day) was included in the JGS list, because this class of drugs are frequently and carelessly used at high doses with calcium preparations for treatment of osteoporosis, leading to hypercalcemia. The result that 37% experienced vitamin D-related ADR justified the inclusion of vitamin D in the list. Regarding additional classes of drugs with more than 10 responses, some drugs of all classes but warfarin were also included in the JGS list. Each drug with many responses should be considered for inclusion when the list is updated.

It is not surprising but important that 93% of geriatricians reduced drugs for the prevention of ADR. This may be a result of educational activities by the JGS and may represent advanced performance of JGS certified geriatricians. Educational efforts and public information to reduce ADR should be strengthened.

The data are not available about what percentage of patients received interventions for drug reduction. We reanalyzed the data of the ADR survey conducted in five university hospitals,[3] and found that the number of drugs were decreased in 20% of inpatients ($n = 1002$) during hospital stay, although the reason for drug reduction is unknown. The investigation of five long-term care facilities[9] showed that one or more drugs were discontinued after admission in 40% of 581 patients on medications. It is noteworthy that the numbers of drugs included in the 1997 version of the Beers list[6] were decreased by 33% (from 61 to 41 cases) in this investigation, even though these drugs were not selectively discontinued. In the future, prospective studies to survey the frequency of drug reduction per patient for ADR prevention, and interventional studies, preferably randomized controlled trials, to investigate the efficacy of drug review/reduction using the JGS version of the Beers list needs to be performed.

Finally, free comments should be appreciated. Various problems and proposals raised from clinical practice are reasonable and were summarized as described in the results section. Other comments included the issue of drug dependency or fear of some patients, effectiveness-biased advertisements by pharmaceutical companies and disease-specific guidelines neglecting the individual difference, leading to the high ADR incidence and inappropriate medication management in elderly patients. Based on the results and comments obtained from this survey, the JGS and geriatricians should promote researches and accumulate the evidence concerning pharmacotherapy in the elderly to develop new guidelines and advance educational activities.

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ORIGINAL ARTICLE

Design of a pragmatic approach to evaluate the effectiveness of concurrent treatment for the prevention of osteoporotic fractures

Rationale, aims and organization of a Japanese Osteoporosis Intervention Trial (JOINT) initiated by the Research Group of Adequate Treatment of Osteoporosis (A-TOP)

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Abstract The aim of osteoporosis treatment is to prevent future fractures. Although concurrent treatment has been used very frequently for osteoporosis in clinical practice, there are no data on accurate and verified effectiveness of concurrent treatment for fracture prevention in patients with osteoporosis. To clarify the clinical usefulness of concurrent treatment, the Japan Osteoporosis Society has authorized the establishment of the A-TOP (Adequate Treatment of Osteoporosis) research group. The objective of this research is to establish a design for a clinical trial to prove whether concurrent treatment using both alfacalcidol (1-alpha-hydroxycholecalciferol) and alendronate is more effective as compared to treatment using alendronate alone

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in terms of fracture prevention. The present study was named JOINT (Japanese Osteoporosis Intervention Trial) and is based on a method using national, prospective, randomized, open-labeled, blinded endpoints focusing on postmenopausal osteoporosis with a high risk for fracture. The patients were mainly selected by practitioners and allocated randomly by a central registration system into two groups, of which one received 5 mg/day of alendronate alone, and the other received 1 μg/day of 1-alpha-hydroxycholecalciferol (alfacalcidol) in addition to the alendronate. The endpoints focused primarily on fracture prevention, and the patients' quality of life (QOL) and change in body height, as well as adherence and the adverse events of the treatments were evaluated secondarily. To obtain sufficient statistical power in the events during a 2-year observation period, the patients who are expected to have higher risk were selected to participate in this study, and it was decided that the final plan would involve 890 patients per group (two-sided alpha = 0.05, power = 0.8). Data collection began in November 2003. Correspondence regarding the registration of the investigator and the progress of the study was conducted through a web system from the Public Health Research Foundation to practitioners.

Keywords Alendronate · Alfacalcidol · Concurrent treatment · Fracture prevention · Osteoporosis

Introduction

Osteoporosis, which is characterized by compromised bone strength and increased susceptibility to fractures, which lead to deterioration in the QOL and increased mortality, is a national burden on an aging society [1, 2]. However, recent studies indicate that treatment with a parathyroid hormone, bisphosphonates or a selective estrogen receptor modulator (SERM) [3–9] may decrease the risk of fractures in patients with osteoporosis.

Although bisphosphonate treatment currently represents the most powerful form of treatment available for fracture prevention in osteoporotic patients, it has not succeeded in completely preventing osteoporotic fractures [3–5, 7–9]. Therefore, concurrent treatment of osteoporosis has been frequently used by Japanese practitioners without any concrete evidence regarding fracture reduction. Since the concept of evidence-based medicine (EBM) has been introduced to clinical practice since the 1990s [10], the Japan Osteoporosis Society and the Japanese Society of Bone Mineral Research have edited the clinical guideline for treatment of osteoporosis (Chief editor: Hajime Orimo [11]). However, the writers recognized that there was a lack of evidence in the effectiveness of concurrent treatment of osteoporosis. Furthermore, it was expected that the patients who visit clinics have varying degrees of risk of fracture, which may differ from the degree of those who participated in development trials for bisphosphonates. This possibility would make it easier to obtain pragmatic evidence in general clinical practice.

Starting in 2000, the Japan Osteoporosis Society had planned to investigate the effectiveness of treatment of osteoporosis in order to provide evidence to general practitioners. Before constructing evidence, some feasibility studies were required to confirm the consensus in the diagnosis of incident fractures among the researchers and to elucidate the risk of future fractures in the patient population. In addition to these efforts in the field of osteoporosis, the Japanese government also established an

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ethical guideline for clinical trials [12], and the International Committee of Medical Journal Editors launched a clinical trial registry [13]. Such kinds of progress in the circumstances of clinical trials have enabled for investigator-initiated clinical trials in general practice.

The Adequate Treatment of Osteoporosis (A-TOP) study group was established in 2000 [11] in affiliation with the Japan Osteoporosis Society and organized a team for clinical trial management. The team consisted of clinical investigators (planning and analysis), foundation (funding) managers, officers from non-profit organization (data management) and several companies (data collection). This was the first joint team to create the post-making evidence for osteoporosis. In November 2003, A-TOP initiated a randomized clinical trial referred to as the Japanese Osteoporosis Intervention Trial (JOINT). The purpose of JOINT was to confirm the clinical significance of concurrent use of osteoporotic drugs. The first protocol, named JOINT-01, was initiated in 2002, but was suspended the following year due to a change in drug labeling. A second protocol, named JOINT-02, was established to clarify the effect of adding 1-alpha-hydroxycholecalciferol (alfacalcidol) to alendronate (ALN), using the incident fracture rate as the primary endpoint. In this paper, the rationale, organization and study design of JOINT-02 are introduced.

Rationale and aims

In 2002, the Japan Society of Osteoporosis sent a letter to randomly selected practitioners and enclosed a questionnaire regarding whether concurrent treatment using bisphosphonate and another drug was being utilized to treat osteoporosis. Surprisingly, 87.8% (79/90 practitioner) of the doctors who responded did have experience using concurrent treatment [14]. The most frequent drugs used in concurrent treatment with amino-bisphosphonate were alfacalcidol (93.7%), followed by calcitonin (50.6%), as there were expectations for these drugs to exhibit more potent inhibition of fracture occurrence or more significant increase in BMD, even though there was no apparent evidence. In addition to the lack of evidence related to fracture prevention, the safety profile of concurrent treatment had not been evaluated. Thus, evaluations of the effectiveness and safety of concurrent treatment were urgently required. Etidronate [15] and ALN [8, 9] were used as the drugs to confirm anti-fracture effectiveness in comparison to alfacalcidol in Japanese osteoporotic patients. However, these clinical trials were carried out at specific institutions and were initiated by experts in accordance with tight regulations. As a result, there may have been differences in the selected treatment and in the backgrounds of the patients between treatments conducted at these institutions and those conducted in general practice. In addition, the adherence of the treatment is expected to be lower in general practice than in institutions with experts who are committed to developmental trials. Thus, pragmatic study is urgently needed to evaluate whether bisphosphonates are effective to the same extent at the level of general practitioners as compared to the prior study (Phase III study).

Feasibility studies

The Japan Osteoporosis Society started discussions to execute a national clinical trial for obtaining evidence regarding the effectiveness of concurrent treatment in 2000. An executive committee of A-TOP was organized in 2002 and planned on forming a consensus regarding judgment standards for pre-existing fractures and incident vertebral fractures [16]. Morphometric criteria for incident fractures combined with a semi-quantitative assessment were thought to provide useful information on the study of clinical osteoporosis, especially for international comparisons. Next, to assume the number of participants in the clinical trial, the incident fracture rate and the risk of incident fracture were analyzed in the patient population, and the number of participants with sufficient statistical power [17] was calculated. Bone resorption marker was an independent risk factor for incident vertebral fractures in Japanese women. When the newly discovered risk factor was incorporated into the inclusion criteria in addition to conventional selection criteria such as age, prevalent fractures and bone mineral density, a reduction of about 40% in the estimated sample size was achieved. Thus, measurement of bone resorption markers is useful in reducing the sample size and the observation period in fracture-prevention studies carried out for developing drugs used to treat osteoporosis.

Materials and methods

Study design

Objective

JOINT was the first national, prospective, randomized, multicenter, open-labeled, blinded endpoints, controlled trial for osteoporosis made up mainly of practitioners of investigators in Japan. The objective of JOINT-02 was to clarify additive efficacy in terms of fracture prevention and safety, QOL and adherence in simultaneous use of alfacalcidol and ALN.

Subjects, intervention and endpoints

Confirmations regarding the patients were made by practitioners based on the inclusion and exclusion criteria (Table 1) after obtaining written informed consent. The

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Postmenopausal osteoporosis[a]
Over 70 years old
Ambulatory patients who do not require any help
Able to answer QOL questionnaire
Corresponds to more than one of A-TOP's risk factors for fracture[b]
Exclusion criteria
Metabolic bone diseases other than osteoporosis[c]
Contraindication to the drugs (ALN or alfacalcidol)
Dysfunction in communication of intentions
Severe degenerative deformation of vertebra
Abnormal heart function
Abnormal hepatic function
Abnormal kidney function
Treatment of osteoporosis by bisphosphonate within 6 months prior to the present study

These thresholds were decided by risk analysis by the A-TOP research group

[a] Over 1 year after menopause

[b] Pre-existing vertebral fracture number ≥ 1; BMD $\leq$ Young Adult Mean -3 SD; Urinary DPD ≥ 7.6 nmol/mmol Cr; or NTX $\geq$ 54.3 nmol BCE/mmol Cr

[c] Hyperparathyroidism and hyperthyroidism were excluded

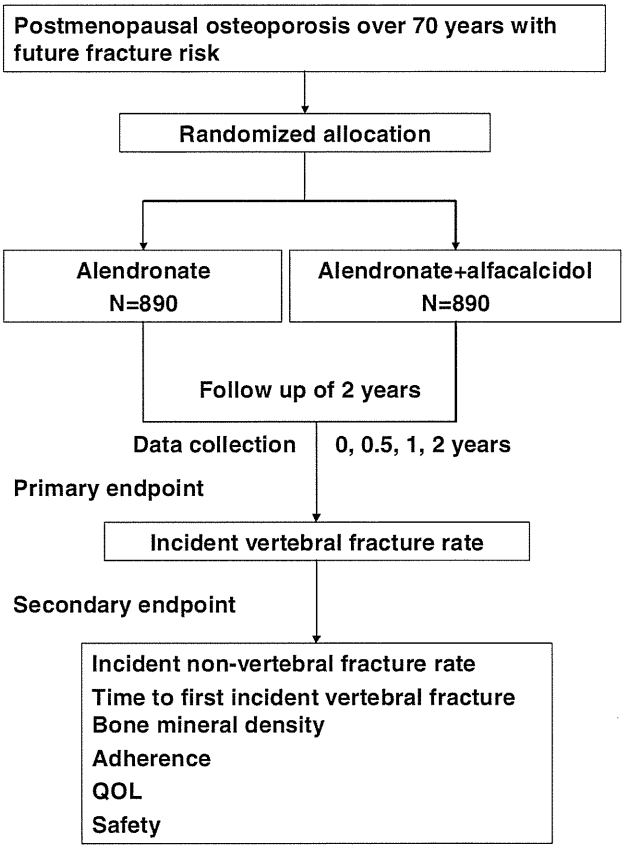

Fig. 1 Study design and outcomes

participants were selected by the practitioners and registered by Japan Clinical Research Support Unit (JCRSU), and then randomly allocated with a modified minimization method using age, number of pre-existing vertebral fracture number, bone mineral density (BMD) and value of bone metabolic marker into the group to be administered only ALN or the group that was to be administered both ALN and alfacalcidol. Registration and allocation of the participants were carried out on the Internet. After initiation of the assigned treatment, clinical data were collected at intervals of half a year for 2 years by I'cros Co., Ltd., through their visiting data collection service. Data were input to the database using a web system developed by ING Corporation. The primary endpoint was to compare the incident vertebral fracture rate between the intervention arms. The secondary endpoints were to compare the differences in the time to first incident vertebral fracture, non-vertebral fracture rate, bone mineral density, adherence, QOL and safety (Fig. 1). In addition, sub-group analyses categorized by baseline characteristics such as age, body mass index (BMI), serum 25-hydroxyl vitamin D levels, the number of pre-existing vertebral fractures and fracture grade were candidate factors. If participants wanted to change the designated treatment because of side effects or occurrence of fractures, they were permitted to do so, and follow-up observations were continued. Please see Table 1 and Fig. 1.

Sample size

Assumptions regarding the fracture rate in the ALN group were made based on a paper by Kushida et al. (Phase III trial for alendronate), in which it is reported that there was a 12.2% fracture rate during observations conducted over 2 years [8]. Since there are not much data on concurrent use of ALN and alfacalcidol [18], the authors' expectations were such that the effects of ALN would be added to those of alfacalcidol and that the hazard ratio of the alfacalcidol combined arm to ALN alone would be 0.64 [19]. The sample size was then estimated to be 890 cases per arm (two-sided alpha = 0.05, power = 0.8), taking account of a dropout rate of 10% referring to the value of the prior clinical trial of fracture intervention [4].

Fracture evaluation

X-ray films of conventional lateral radiographs of lumbar and thoracic vertebrae were taken and collected by I'cros Co., Ltd. After masking the patient's information, two

independent readers (orthopedist, TN and radiologist, MF) simultaneously reviewed films from T4 to L4 in chronological sequence and graded vertebral fracture based on a semi-quantitative method [20]. Before the start of the study, these two observers held meetings to make adjustments between their own criteria for grading vertebral fractures. When the diagnosis of pre-existing fractures made by the reviewers differed from those made by the practitioners, the reviewers' diagnosis was adopted preferentially. If inconsistencies arose between the readers in diagnosing pre-existing and incident vertebral fractures, the two readers negotiated between themselves to reach a consensus. Incident bone fractures other than those of the vertebrae were comprehended from the chart, and the occurrence of fractures was confirmed based on X-ray films or a record of the operation.

Clinical data

BMD at the lumbar vertebrae, hip (proximal femur), distal radius (dual energy X-ray absorptiometry) or left-sided second metacalpal bone (microdensitometry) was measured at baseline and at 6-month intervals for 2 years at each institute. The data of BMD obtained from the different machines and from different bone sites were calculated as the percentage change in each time point from the baseline value. The statistical difference in change of BMD between the group that received combined treatment and the group that was administered only ALN was compared based on each set of data for BMD for the different bone sites. Body height was measured at baseline, 12 and 24 months. Bone turnover markers (urinary type I collagen cross-linked N-telopeptide or urinary excretion of deoxypyridinoline) were measured at baseline and again 6 months after initiating treatment. QOL was assessed by using self-administered questionnaires (JOQOL and EQ-5D) at baseline and at 6, 12 and 24 months after initiating treatment [21]. Serum samples were sent to the central laboratory (SRL Co., Japan), and 25-hydroxyl vitamin D concentrations were measured. Other routine biochemical examinations were carried out at baseline and at 2 years after initiating treatment in order to estimate biochemical adverse events. All adverse events were reported to JCRSU, coded by MedDRA, and categorized as either "known" or "unknown." If an unknown adverse effect occurred, it was reported to the investigator and ethical committee.

Ethics and registration

Ethical issues regarding protocol were reviewed by the ethical committee for JOINT under the Declaration of Helsinki (Dr. Rikushi Morita, Chairman). If it turned out that a patient was at a disadvantage under observation, the ethical committee was given permission to stop the protocol. This study was registered at UMIN-CTR (University Hospital Medical Information Network—Clinical Trial Registry) with the number C000000001.

Statistical analysis

Analysis of the intent to treat principle was applied to the statistical analysis. Efficacy analysis uses a full analysis set (FAS), and all of the enrolled patients are applied to the analysis except for patients without efficacy data, patients who do not correspond to inclusion criteria and patients who do not receive treatment. The PPS (protocol per set) group is defined as consisting of patients without any serious protocol violation.

Recruitment of the practitioner

The explanatory meeting of the protocol and registration was held in all of Japan. The executive members of the A-TOP research group were responsible for the presentation of the protocol and for the recruitment of study institutions and practitioners. The A-TOP committee created the WEB site on the Internet so that the registration of the study could be executed directly. I'cros Co., Ltd., was also involved as a collaborator in calling practitioners.

Results and discussion

Several principles had to be considered for acceptance of concurrent treatment: firstly, the concurrent treatment should be clinically and statistically significantly more effective than the basic treatment; secondly, the concurrent treatment should be of the same level of safety as single treatment; thirdly, the concurrent treatment should be cost-effective. Although these principles should be evaluated before adopting concurrent treatment, the authors have applied concurrent treatment to osteoporosis widely, without any background evidence. Among these principles, the authors have decided to evaluate the first two issues, effectiveness and safety, in the present study. Since this type of evaluation is absolutely required by a clinician, a researcher-initiative study was considered as being the most suitable type of evaluation. This was the reason why the authors decided to use a researcher-initiative clinical trial in determining the effectiveness of concurrent treatment for osteoporosis. The JOINT-02 protocol was the first randomized, controlled trial conducted nationwide for osteoporosis in Japan initiated by researchers, and its scale was also the largest ever. It was therefore necessary for various organizations to collaborate together, and there

have been no previous reports on how to manage the PROBE trial in Japan. This is why we wanted to report the design of JOINT-02. In this paper, we have presented the organization of the A-TOP research group and execution of the JOINT 02 protocol. This is because we believe that this report should help a researcher who is willing to build a new nationwide investigation that is constructed by an organization of clinical research work.

Since the primary aim of JOINT-02 was to determine whether concurrent treatment using ALN and alfacalcidol is superior to treatment using ALN alone in terms of fracture prevention, true ("hard") endpoints such as vertebral fractures or long bone fractures were selected as the primary endpoint. The diagnosis of whether vertebral fractures were present or not on the X-ray films was made by two independent reviewers who did not have any information about the patient; when the judgment of fractures was split between the two reviewers, the reviewers negotiated with each other. Identifying vertebral fractures is more difficult than identifying long bone fractures due to some cases of new vertebral fractures not showing clinical symptoms and the shape of the vertebral body making it difficult at times to recognize whether there is a fracture. Therefore, to avoid misdiagnosis, diagnosis of pre-existing and incident vertebral fractures was made by two different observers. In cases where there was a discrepancy in the diagnosis of vertebral fractures between the reviewers and the practitioner, which occurred with regard to pre-existing fractures, the reviewers' judgment was given priority over that of the practitioner.

Surrogate ("soft") endpoints such as change in BMD or bone turnover markers were considered to be inadequate as primary endpoints in making conclusive statements regarding the efficacy of concurrent treatment. In this type of study, the soft endpoint (BMD or biomarkers) will connect dropout bias less effectively than the case-selected hard endpoint, because such markers are not able to be made blind to the clinicians. Furthermore, previous studies indicate that changes in BMD or bone markers do not predict future fractures [22–24].

In recent literature, it has been reported that poor adherence of bisphosphonates leads to a decline in the beneficial effects of this drug on bone [25–28]. It is expected that in contrast to prior developmental trials, this current study may have a higher dropout rate, since in a researcher-initiative study, the registered practitioner is not forced to maintain adherence very strictly. As a result, adherence in the present study may resemble the actual circumstances of adherence to bisphosphonate treatment by a general practitioner. It will be interesting to determine whether adherence in this study modifies fracture prevention by alendronate.

Although a careful plan for this study has been set up, the results will be applied to osteoporosis patients with the same background as the present study population, but not adapted to the entire osteoporosis population. Despite this limitation, we believe that the results will give us very important information regarding the concurrent treatment of osteoporosis.

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LETTER TO THE EDITOR

Actions of the Japan Geriatric Society in response to the 2011 off the Pacific Coast of Tohoku Earthquake: First report

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Dear Editor,

A huge earthquake occurred in Japan on March 11, 2011 at 2:46 PM (Japanese standard time). The Japan Meteorological Agency officially announced that this earthquake was named the "Off the Pacific Coast of Tohoku Earthquake" and had a magnitude of 9.0. This disaster presented several unique characteristics compared to previous earthquakes in Japan, including the great Hanshin-Awaji earthquake, because it brought about a large tsunami, resulting in exceptional damage in the northeast-east areas of Japan and destruction of many coastal cities.[1] According to the report by the National Police Agency of Japan, 15 413 people died as of June 11, approximately 90% of them drowned. In addition, the huge tsunami disaster took an unexpected turn, with 8069 persons still missing. This terrible disaster shows the uniqueness of this earthquake. Approximately 470 000 people had to be evacuated to shelters as a result of unavoidable circumstances at the peak (on 14th March), and around 100 000 people are still living in shelters. In addition, the huge tsunami unexpectedly resulted, not only in widespread destruction of communities, but also in nuclear power plant accidents in Fukushima, leading to the collapse of daily life of many residents.

The Japan Geriatric Society (JGS) immediately formed the Disaster Supportive Center on 18th March 2011 and took several steps to deal with this huge disaster. First, the JGS grappled with the issue of geriatric medicine in the disaster, in cooperation with the Study Group of the "Guidelines Regarding the First Steps and Emergency Triage to Manage Elderly Evacuees". In the case of elderly victims, even after their safe evacuation to a refuge, it is possible that they may suffer from disaster-related illnesses, including the deterioration of pre-existing illnesses, cerebro-cardiovascular disease, infectious disease, and mental stress. In general, these disaster-related illnesses are induced by numerous factors, such as psychological distress, dehydration, and sympathetic nerve hyperactivation, and can lead to fatal and non-fatal conditions. Simultaneously with establishing the guidelines, the Study Group and JGS also made a manual for non-medical care providers (NMCP; e.g. public health nurses and certified social workers). The aim of this simple manual was to help NMCP and/or the families of the elderly to quickly identify illnesses in elderly evacuees. The booklets were distributed to a widespread stricken area, mainly Iwate, Miyagi, and Fukushima prefectures, by JGS members and Japan Medical Association Teams in each prefecture. Therefore, our mission in the JGS, using both the guidelines and the manual, was to extend life-saving medical help to as many elderly evacuees as possible via the reduction of susceptibility to disaster-related illnesses and death.

Next, the JGS Supportive Center immediately decided to dispatch a medical support team to a refuge in Soma City, Fukushima, as well as visit Ishinomaki and Higashi-Matsushima, Miyagi, to investigate the damage situation for elderly victims. In addition, the JGS also sent a support team of physicians to Mitsuke, Niigata, which shares a border with Fukushima prefecture. Mitsuke City, with 42 500 residents, accommodated around 500 refugees in three shelters. Most of the refugees were from Minami-Soma City where it had been recommended that people evacuate because of the nuclear power plant accidents. Since Mitsuke City itself has been struck by natural disasters twice in the last 10 years, but had no damage from the earthquake this time, the quality of support to refugees here was quite

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different from that in the center of the area struck by the earthquake and tsunami (Abe Y *et al.,* unpubl. data. manuscript in preparation).

Now, beyond the chronic phase, elderly evacuees are being gradually shifted from shelters to temporary housing. However, it is possible that they may have serious new problems, they might lose stimulation from the outside world and become miserable (e.g. survival guilt and nightmares). These emotional changes may lead to a decline in cognitive function and disused muscle atrophy of their extremities while in temporary housing. Another goal of JGS is to prevent a decline in the cognitive and functional abilities of the elderly in the long term through multidisciplinary support. The JGS needs to carry out a longitudinal investigation to clearly address the psychological distress and somatic symptoms in elderly victims based on posttraumatic emotional stress with exposure to disastrous conditions. In addition, the development of a national disaster plan for mental health in the elderly may also be required.

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