

# Sequential versus Combination Treatment Using Steroids and Diuretics for Acute Low-Frequency Sensorineural Hearing Loss: A Noninferiority Trial

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**Objective:** Acute low-frequency hearing loss (ALHL) is typically treated with combination therapy, including steroids and diuretics. To avoid unnecessary use of steroids we proposed a method of sequential administration using these two drugs, and compared the efficacy of our protocol with that of existing combination treatments.

**Methods:** A prospective, randomized, open-label, single-blind, noninferiority clinical trial was conducted to investigate whether the effectiveness of sequential treatment is noninferior to that of combination treatment for ALHL. Ninety-two patients with ALHL received either steroids and diuretics simultaneously for 2 weeks (combination group), or diuretics for 2 weeks followed by steroids for another 2 weeks if they did not respond to diuretic treatment (sequential group). The primary outcome measure was a change in mean hearing threshold at three frequencies (125, 250, and 500 Hz) at 4 weeks after treatment.

**Results:** The mean hearing threshold of the low frequencies improved 20.0 and 17.2 dB in the combination and the

sequential group, respectively. The 95% lower confidence interval was  $-8.0$  dB and noninferiority was established at  $p < 0.05$ . At 4 weeks after treatment, the complete recovery rate was 80.5 and 82.9% in the combination and sequential groups, respectively.

**Conclusion:** This is the first study on ALHL treatment following the establishment of Consolidated Standards of Reporting Trials (CONSORT). The sequential treatment is not inferior to combination treatment for ALHL, and therefore may be a better treatment guideline for ALHL considering that patients receive less steroid exposure and smaller restrictions in diuretic use compared with steroids.

**Key Words:** Acute low-frequency hearing loss—Combination treatment—Diuretics—Noninferiority—Sequential treatment—Steroids.

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Abe (1) first distinguished acute low-frequency sensorineural hearing loss (ALHL) from idiopathic sudden sensorineural hearing loss (SSHL), as being limited to low frequencies and showing better treatment outcomes and spontaneous recovery rates. Although the treatment of ALHL continues to develop, no standard protocol has been established thus far. ALHL etiology has been attributed to both endolymphatic hydrops and an auto-immunological mechanism (2–4). As such, aggressive combination treatment using steroids and diuretics has been widely encouraged (5–12).

Glucocorticoids, however, are known for their potential and severe side effects in many organ systems (13–15). As

a result, use of the steroids is contraindicated in patients with certain systemic conditions, such as insulin-dependent or poorly controlled diabetes, labile hypertension, tuberculosis, and peptic ulcer disease (16,17). Furthermore, simultaneous administration of steroids and diuretics (combination treatment) may induce unwanted drug interactions that affect sodium and water metabolism. Diuretics alone, however, are considered safer to use, although hypokalemia, hyponatremia, hypercalcemia, hyperglycemia, and gout have been reported in association with them (18–20).

If steroids could produce a salvage effect for ALHL patients who did not recover on treatment with diuretics alone, we might expect comparable efficacy to combination therapy using a sequential approach. In doing so, we would be able to avoid unnecessary steroid use by reserving these medications for salvage cases only. We performed a prospective, randomized, noninferiority trial in which we compared the treatment outcomes between patients who received simultaneous steroids and diuretics (combination/reference treatment) to those who received diuretics first, followed by steroids as a salvage therapy

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(sequential/experimental treatment), for the treatment of ALHL. A noninferiority trial was warranted because combination treatment is an established intervention for ALHL with a reported clinical superiority over placebo (11,12); diuretics alone or steroids alone have been shown to have a comparable efficacy, albeit slightly smaller, to combination treatment (6,11,12); and sequential treatment offers the advantages of reduced steroid exposure and fewer adverse effects.

## PATIENTS AND METHODS

### Study Design

We conducted a prospective, randomized, open-label, single-blind, noninferiority clinical trial to compare the efficacy of sequential versus combination therapy for ALHL, following CONSORT standards. All patients provided written informed consent after a full explanation of the study protocol. This study was approved by the institutional review board of Kangwon National University Hospital.

### Patients

We used the diagnostic criteria for “definite” ALHL as proposed by the Study Group for the Acute Profound Deafness Research Committee of the Ministry of Health, Labour and Welfare of Japan (21). Diagnostic criteria are as follows: pure SSHL without vertigo; unknown cause; the sum of pure-tone hearing levels at low frequencies of 125, 250, and 500 Hz is 70 dB or more; the sum of pure-tone hearing thresholds at high frequencies of 2000, 4000, and 8000 Hz is 60 dB or less (10,11). All patients underwent an initial examination including documenting their medical history; conducting a physical examination, otoscopic examination, pure-tone audiometry (PTA), speech audiometry, impedance audiometry, immunological tests, serological tests, and/or an imaging study such as computed tomography or magnetic resonance imaging; and analyzing distortion product otoacoustic emissions, blood data including a full blood count, and blood biochemistry. Inclusion criteria consisted of “definite” ALHL, symptom duration of 14 days or less before treatment initiation, and age more than or equal to 18. Patients were excluded from the study if they were pregnant; had a health condition that precluded the use of either a steroid or diuretic (such as active, ongoing inflammatory diseases; a history of hepatitis B or C, human immunodeficiency virus, or any active systemic infection within the 2 weeks before baseline; diabetes; gastritis; malignancy; active tuberculosis; glaucoma; osteoporosis; hyperglycemia, etc.); had a previous history of any other ear disease including chronic otitis media, noise-induced hearing loss, ototoxic drug-induced hearing loss, head trauma, head and neck radiation therapy, ear barotrauma, retrocochlear disease, or inner ear malformation; or had any history of metabolic, hematological, psychiatric, renal, hepatic, pulmonary, neurological, endocrine, cardiac, autoimmune, infectious, or gastrointestinal conditions such as diabetes mellitus, cerebral infarction, chronic heart or renal diseases, hypo or hyperthyroidism, or dementia, which, in the opinion of the investigator, placed the patient at unacceptable risk for participation.

### Study Interventions

The sequential group received oral diuretics (25 mg/d hydrochlorothiazide and 40 mL/d isosorbide solution) during the initial 2 weeks. Patients who did not completely recover after this treatment (complete recovery was defined when each of the

three low-tone frequencies of the final PTA was  $\leq 20$  dB) underwent 2 more weeks of additional steroid-only treatment (0.8 mg/kg/d of oral methylprednisolone for 7 days, gradually tapered for the next 7 days). The combination group received both diuretics and steroids simultaneously for 2 weeks, with both drugs administered at the same dosages as in the sequential group; the medications were stopped after 14 days regardless of hearing recovery. All patients in both groups underwent follow-up PTA on day 14 and 28.

### Randomization and Allocation Procedures

The audiologist who performed hearing test was blinded to the prescribed drugs, while the participants were not. Patients were randomly assigned to one of two groups at a 1:1 ratio using a computer-generated list of random numbers only accessible by a statistician. At the time of group allocation, the clinician who recruited the patients contacted the statistician to inquire about the next patient’s allocation.

### Outcome Measures

The primary outcome variable was the change in the mean hearing thresholds of the three low frequencies (125, 250, and 500 Hz) between pretreatment and follow-up at 4 weeks ( $\Delta$ MeanLow). The secondary variable was recovery rate, with complete recovery (CR) defined as when each of the three low-tone frequencies of the final PTA was 20 dB or less. Partial recovery (PR) was defined as the mean PTA of the three low frequencies improving by more than or equal to 10 dB compared with the initial value. No recovery (NR) was defined in all other cases (21).

### Statistical Analyses

The primary null hypothesis was that sequential therapy is inferior to combination therapy for the treatment of ALHL. We defined noninferiority of the sequential treatment if  $\Delta$ MeanLow of the combination group at 4 weeks exceeded that of the sequential group by 10 dB HL, because the same definition was previously used in another noninferiority trial that compared two steroid treatments for SSHL (22). Furthermore, 10 dB exceeds the test–retest variability of the PTA audiogram, which was one 5 dB audiometric step (23). The next standard audiometric step (10 dB) is considered the smallest change boundary for clinical reporting of asymmetries and air-bone gaps for clinical test procedures (24). Therefore, the null hypothesis was  $\mu_1 - \mu_2 \leq -10$ , where  $\mu_1$  and  $\mu_2$  are means of the primary variables of the sequential and combination treatment, respectively.

The noninferiority analyses were conducted using both intention-to-treat and per-protocol methods. Intention-to-treat analyses were performed in three different ways: 1) the last available data of missing subjects were carried forward to 4 weeks, 2) all missing subjects were considered CR and their PTA values at each of the low frequencies were set to 20 dB (minimal value to consider them CR), and 3) subjects that dropped out due to early hearing recovery were considered CR, while all other subjects had their last available data used. The per-protocol analyses were performed on patients who completed all 4 weeks of follow-up. For each of these analyses, the null hypothesis was evaluated using a one-sided *t* test at the 95% confidence level.

All other analyses were performed using a per-protocol base. All other continuous outcomes were assessed using two-sided, two-sample *t* tests for a standard null hypothesis of no difference between means. Categorical variables were compared using the  $\chi^2$  test. *p*-Values  $< 0.05$  were considered statistically significant.

Sample size calculations assumed a 5% one-sided  $\alpha$ , 90% power, 1:1 allocation ratio, noninferiority margin of 10 dB, and a standard deviation of  $\Delta$ MeanLow of 15.0 (the standard deviation was determined during the interim data analysis after 20 patients were recruited in each group). The number of patients in each group was estimated to be 40. Considering a 10% dropout rate, the total sample size was calculated to be 88. The actual standard deviation and dropout rates were 14.3 and 10.9% (10 out of 92), respectively.

SAS 9.4 (SAS Institute Inc., Cary, NC) was used for all statistical analyses.

**RESULTS**

**Patients**

A total of 121 patients with ALHL were screened through the otolaryngology outpatient clinic of our

hospital from April 2017 to June 2018; 29 patients were excluded for not meeting eligibility criteria (Fig. 1). The remaining 92 patients consented to participate and were subject to randomization (47 into combination and 45 into sequential group). Ten participants withdrew from the study (six combination, four sequential) before the first follow-up. Overall, 41 participants in each group completed a full course of medication and attended all 4 weeks of follow-up. There were no significant adverse effects reported by patients who completed the treatment in either group. In the sequential group, 28 patients completely recovered by 2 weeks using diuretics alone, while the 13 patients who did not recover subsequently underwent further treatment with 2 weeks of steroids. Per-protocol analyses were performed on the 82 subjects who completed

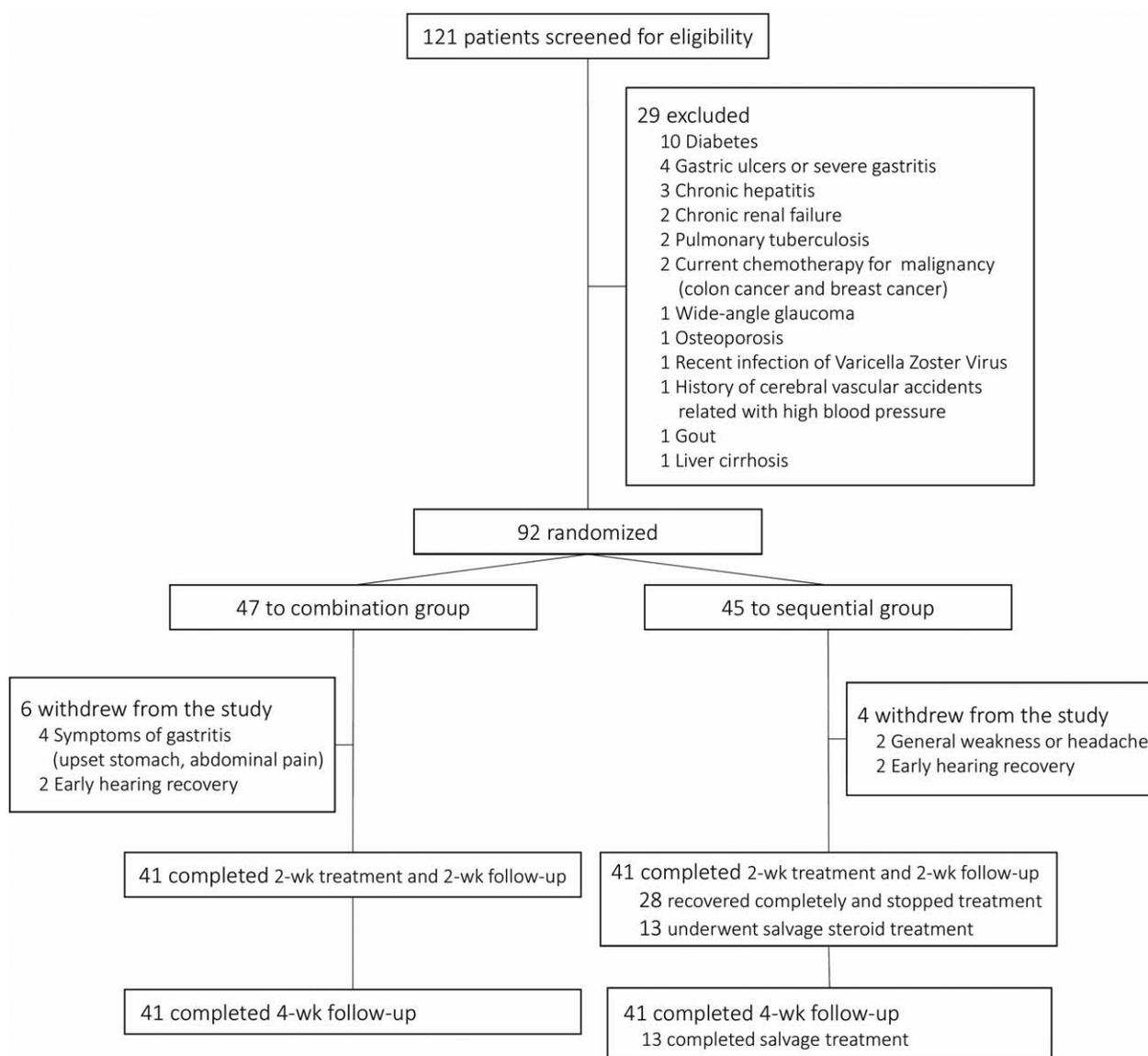


FIG. 1. Illustration of the study flow.

**TABLE 1.** Demographics and baseline hearing profiles of ALHL patients<sup>a</sup>

Characteristics	Combination (N = 47)	Sequential (N = 45)
Demographics		
Age (yr) <sup>b</sup>	46.5 ± 13.5	44.4 ± 11.8
Sex (M:F) (%)	36:64	31:69
Hearing loss		
Hearing loss onset before study entry (dB HL)	7.2 ± 4.4	7.4 ± 3.9
Laterality of diseased ear (R:L) (%)	55:45	40:60
Sum of three low frequencies (dB HL)	108.7 ± 35.6	97.5 ± 31.2
Mean of three low frequencies (dB HL)	36.2 ± 11.9	32.5 ± 10.4

<sup>a</sup>There were no significant differences in baseline characteristics between the combination and sequential treatment groups.

<sup>b</sup>Continuous variables are expressed as mean ± standard deviation.

ALHL indicates acute low-frequency sensorineural hearing loss; F, female; HL, hearing level; L, left; M, male; R, right.

a full course of medication and attended 4-weeks of follow-up.

There were no significant differences in the baseline demographic characteristics or hearing measures between two groups (Table 1).

### Primary Outcome Analyses

The intention-to-treat analyses results are summarized in Table 2. The rest of the figures and tables represent per-protocol analyses results.

ΔMeanLow in the sequential group was not inferior to that of the combination group in any of the analyses (Table 2). In the intention-to-treat analyses with initial values carried forward for all dropped-out participants, ΔMeanLow was 20.0 dB in the combination group and 17.2 dB in the sequential group. Because the absolute value of the 95% lower CI (−8.0 dB) was smaller than 10 dB (noninferiority margin), sequential treatment demonstrated noninferiority to combination treatment. Similarly, the other two intention-to-treat analyses had a lower CI of −8.8 and −8.1 dB. In per-protocol analyses, the lower CI was −9.0 dB and the ΔMeanLow difference between groups was 4 dB. All noninferiority analyses rejected the null hypothesis at  $p < 0.05$  and confirmed that sequential treatment is not inferior to combination treatment.

### Hearing Recovery Rate

In the combination group, 31 patients (75.6%) had CR, 3 (7.3%) had PR, and 7 (17.1%) demonstrated NR after 2 weeks of treatment. In the sequential group, 28 (68.3%), 4 (9.8%), and 9 patients (22.0%) showed CR, PR, and NR at 2 weeks, respectively (Fig. 2). Between 2 and 4 weeks, two out of 10 patients who did not show CR (20.0%) in the combination group, and six out of 13 (46.2%) patients in the sequential group eventually attained CR (Fig. 3B). Lastly, at 4 weeks we found CR, PR, and NR in 33 (80.5%), 3 (7.3%), and 5 (12.2%) patients in the combination group compared with 34 (82.9%), 2 (4.9%), and 5 (12.2%) patients in the sequential group (Fig. 3A).

The ΔMeanLow of patients who did not show CR was  $3.2 ± 15.7$  and  $7.1 ± 13.2$  dB at 2 weeks and  $10.3 ± 22.6$  and  $13.2 ± 14.9$  dB at 4 weeks in the combination and sequential groups, respectively. The change in ΔMeanLow for patients who initially failed at 2 to 4 weeks was statistically significant for the sequential but not the combination group (two-sample  $t$  test,  $p < 0.05$ ,  $N = 10$  combination,  $N = 13$  sequential).

### DISCUSSION

The etiology of ALHL is proposed to be secondary to endolymphatic hydrops or an autoimmune mechanism

**TABLE 2.** Noninferiority analyses comparing the mean hearing improvements using combination or sequential treatment

Analyses	N (Comb: Seq)	Combination ΔMeanLow	Sequential ΔMeanLow	Noninferiority $p$ -Value	Lower CI
Per protocol	41:41	22.9	18.9	0.0291	−8.959
Intention-to-treat					
All NR	47:45	20.0	17.2	0.0119	−8.008
All CR	47:45	22.4	18.5	0.0208	−8.817
Early recovery CR	47:45	20.4	17.4	0.0126	−8.113

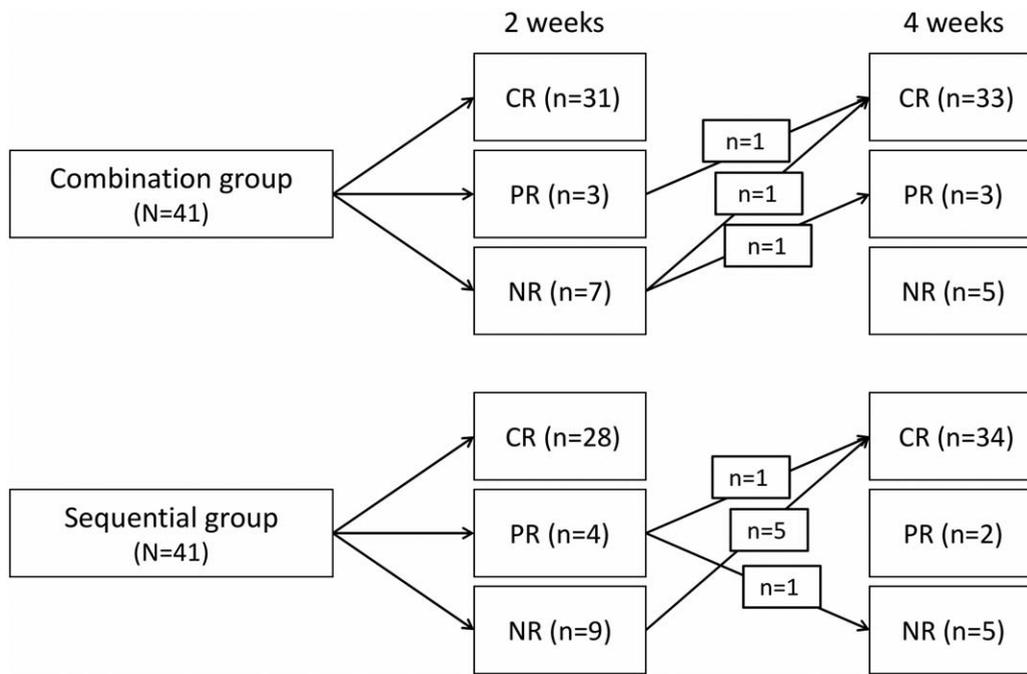
ΔMeanLow indicates change in the mean hearing thresholds of the three low frequencies between pretreatment and follow-up at 4 weeks; CI, confidence interval; Comb, combination treatment; CR, complete recovery; NR, no recovery; Seq, sequential treatment.

All NR: the baseline data were used for all missing patients.

All CR: all missing patients were considered CR.

Early recovery CR: patients that dropped out because of early hearing recovery were considered CR; for the rest of the subjects their last available data were used.

Based on all intention-to-treat analyses and per-protocol analyses, the null hypothesis of inferiority was rejected at  $p < 0.05$ . 95% lower CI was greater than −10 dB for all analyses.

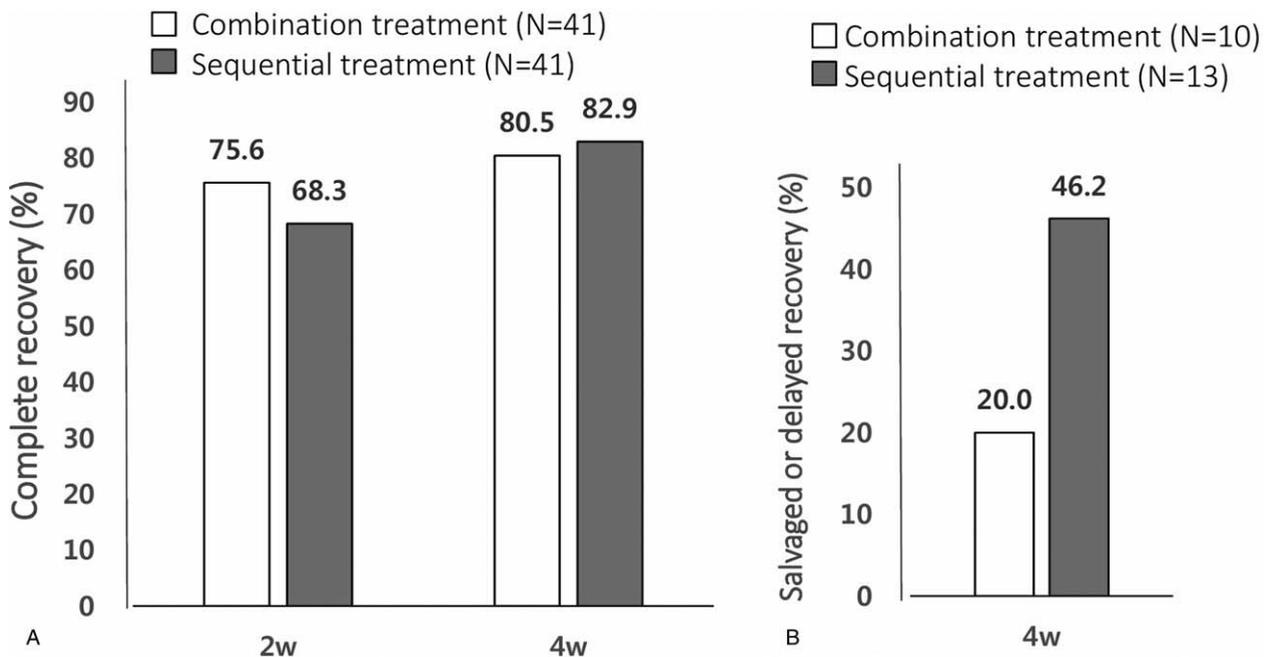


**FIG. 2.** Schematic of recovery flow from 2 weeks to 4 weeks of treatment. CR indicates complete recovery; NR, no recovery; PR, partial recovery.

(2,16,25–27). As such, steroid–diuretic combination therapy is expected to produce better hearing recovery rates compared with other treatments (8–12). CR rates in previous studies have been found to be 63 to 83% with diuretics alone, 42 to 79% with steroids alone, and 60 to 78% with a combination of both medications (4–11). In our study, CR rates were 80.5% in the combination group

and 82.9% in the sequential group, which is comparable to the highest levels previously obtained by other studies using combination therapy.

In some previous studies, high-dose steroids were administered as a salvage attempt after low doses had initially failed (4,12). However, high-dose steroids have a considerable side effect profile, as shown in a previous



**FIG. 3.** Incidence of complete recovery for all patients at 4 weeks (A), and for patients who failed initial treatment (B).

SSHL study that found adverse effects in 33.0% of 500 patients who received short-term high-dose steroid therapy (22). Therefore, given the noninferiority of sequential treatment as demonstrated in our trial, we think that sequential (and selective administration of steroids) therapy presents itself as a more desirable option for ALHL treatment, because there is potentially less exposure to steroid medications.

To the best of our knowledge, this is the first trial to investigate the effects of sequentially administering diuretics and steroids. All patients in our study started the treatment within 14 days after disease onset. Two weeks of additional steroids were given for 13 patients in the sequential group who did not have CR, and six (46.2%) of them were subsequently salvaged to attain CR at 4 weeks. Although the duration of symptoms before treatment were claimed to be a significant factor affecting hearing recovery rates (7,10,12,21) Alatas et al. (28) reported that the average ALHL recovery rates 0 to 7, 8 to 20, and after 20 days from time of symptom onset were 89.4% (64–100), 88.3% (71–100), and 37.3% (17–48), respectively. On the other hand, the average duration of ALHL before treatment initiation was 13.5 days in a recent nationwide epidemiological survey of Japan that included 931 ALHL patients (6). That study reported a CR rate of 72.0% in the systemic steroid group and 83.1% in the diuretic-only group. The above studies demonstrate that treatment can be successful even if it is started 14 days after symptom onset. In our study, almost half of the patients who initially failed were able to achieve CR using sequential treatment, while only 20% were able to do so in the combination group, through either spontaneous recovery or possibly prolonged/delayed action of the steroid. Furthermore, the mean hearing improvement from 2 to 4 weeks was significant for the sequential group but not for the combination group. These results suggest that the conversion to CR during the steroid-salvage period in the sequential group might not be attributable to spontaneous recovery or delayed effects from the initial drug. The last 2 weeks of salvage steroid therapy seemed quite effective in our trial, which indicates that ALHL is correctible even after 14 days from onset of symptoms. Complete spontaneous recovery for ALHL has been reported to be 40 to 60% (3,11,29), and these considerably high rates could also rationalize the use of a more conservative approach, sequential treatment.

This study had some limitations. First, we did not include any placebo for the combination group from 2 to 4 weeks. Placebo is known to have a positive therapeutic effect in 21 to 56% of the patients, depending on the study type (30). Therefore, the fact that non-recovered patients in sequential group received medication for 4 weeks, while those in combination group only for 2, could have contributed to differences in the CR rate during final 2 weeks. Second, because ALHL may be recurrent or progress to Ménière's disease, further long-term follow-up studies are needed to compare the final efficacy of both treatments to make sure that the treatment result was not reversed or progressed to another disease with time.

## CONCLUSIONS

Sequential treatment for ALHL is not inferior to combination treatment. We think that a sequential approach may be a safer, better treatment guideline for ALHL, particularly when considering the severe adverse effects related to high-dose or long-term steroid use.

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