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Guest Editorial

To Treat or Not To Treat Renal Anemia of Chronic Kidney Disease Patients?

In Japan, recombinant human erythropoietin (rHuEPO) became available for patients undergoing hemodialysis (HD) in 1990. Approximately 80% of the patients were soon given the benefits of the novel product. It became available also for patients of non-dialysis chronic kidney disease (CKD) and its efficacy has been established as well.

The therapeutic target of hemoglobin (Hb) level is still controversial. In 1998, the results of the US Normal Hematocrit Study on HD patients were reported (1). The high hematocrit (Ht) group from this study showed unfavorable tendencies in survival time and incidence of myocardial infarction, and the trial was discontinued in line with these findings. Interestingly, it was also reported that the mortality in patients showing lower Ht was higher in both groups. The K/DOQI guidelines 2001 edition, however, recommended a target Hb level of 11–12 g/dL, in line with the safe levels identified in the Normal Hematocrit Study (2).

In Japan, the first working group for the Renal Anemia Treatment Guideline was formed with Professor F. Gejyo as the chairman in 2001; however, there was no available evidence studying Japanese patients. Although the recommended target Hb levels are the same for both HD patients and CKD patients in the US and Europe, it was suggested from statistical analysis by the Committee on Renal Data Registry (CRDR) of the Japanese Society for Dialysis Therapy (JSDT), that HD patients should not be treated in the same way as peritoneal dialysis and CKD patients since they show marked changes in Hb levels before and after HD. Under the above circumstances, guidelines for HD patients only were published in Japan in 2004, employing the target Hb level as 10–11 g/dL, which was lower than those recommended in the Western guidelines (3).

In 2005, the second working group for the Renal Anemia Treatment Guideline was formed with myself as chair and completed the new guidelines, including CKD patients in the 2008 in Japanese edition (4). (The English-translated version appears in this issue).

The target Hb levels were revised to 11 g/dL or greater (upper limit of 14 g/dL; for patients with serious cardiovascular complications the upper limit was 12 g/dL) in the 2004 European Best Practice Guidelines (EBPG) (5) and to 11 g/dL or greater (upper limit of 13 g/dL) in the 2006 K/DOQI guidelines (6).

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study (7) provided major impacts on the target Hb levels. In the results of the ITT analysis, the onset of cardiovascular events was significantly higher in the high Hb group. In a comparison of the characteristics of patients in the CHOIR study and those of patients at introduction of HD in the observational Japan Erythropoietin Treatment (JET) study, the percentage of patients with cardiovascular disease (CVD) in the CHOIR study was much higher than in the JET study (8) (Table 1). In CHOIR, a great deal of the onset of CVD might be observed in such a high risk group; therefore, it is hard to employ in clinical practice to low risk patients. The JET study is expected to provide further evidence based on a different population.

rHuEPO resistance was reported to be closely involved in the onset of CVD events (9). Furthermore, the use of high dose rHuEPO was the most potent factor predicting the poor prognosis. The relation between high Hb levels and poor prognosis could not be confirmed by the secondary analysis of CHOIR (10). It was also reported that most cardiovascular complications occurred during the hemoglobin cycling, especially when Hb revealed a sharp decrease (9). Taken together, it is suggested that patients with serious CVD or other diseases requiring high doses of rHuEPO might have a poor prognosis (11).

Based on the results of the CHOIR, the FDA immediately recommended that the Hb level of patients treated with erythropoiesis stimulating agents (ESAs) should not exceed 12 g/dL. In the K/DOQI guidelines, the upper limit of the target

TABLE 1. *The comparison of patient characteristics in each study*

Group	TREAT (N = 4038)		CHOIR (N = 1432)		JET (N = 1949)	
	DA (N = 2012)	Placebo (N = 2026)	High Hb (N = 715)	Low Hb (N = 717)	Anamnesis/treatment history	Complication
Target Hb (g/dL)	13	>9	13.5	11.3	–	–
Mean Hb (g/dL)	12.5‖	10.6‖	12.6	11.4	–	8.0
Baseline characteristics of the patients						
Hypertension (%)	90*	89.8*	95.8†	93.2†	–	70.8
History of CVD (%)	64.0†	66.9†	–	–	–	–
Coronary artery disease (%)	43.2	45.5	–	–	–	–
Myocardial infarction (%)	18.4	18.3	16.4	15.0	3.6	1.1
CABG (%)	–	–	17.4†	13.5†	2.4	–
PCI (%)	–	–	10.9	11.9	4.5	–
Heart failure (%)	31.5†	35.2†	24.4	22.9	5.4	10.2
Atrial fibrillation (%)	11.0	10.0	9.4	8.6	1.5¶	3.4¶
Stroke (%)	11.5	10.7	9.8	10.0	12.6§	2.9§
PAD (%)	21.2	20.8	16.4	16.4	1.4	3.5
Malignancy (%)	9.3	7.9	–	–	–	–

CABG; coronary artery bypass grafting,PCI; Percutaneous coronary intervention, PAD; Peripheral arterial disease
‖; Median Hb, *; ACI and/or ARB prescription, †; significant difference between two groups; ¶; arrhythmia, §; cerebrovascular disease (including asymptomatic patients).

level was revised from 13 g/dL to 12 g/dL in less than a year (12). Also, the upper limit in the European Renal Best Practice (EBPG) was recommended as 12 g/dL (13).

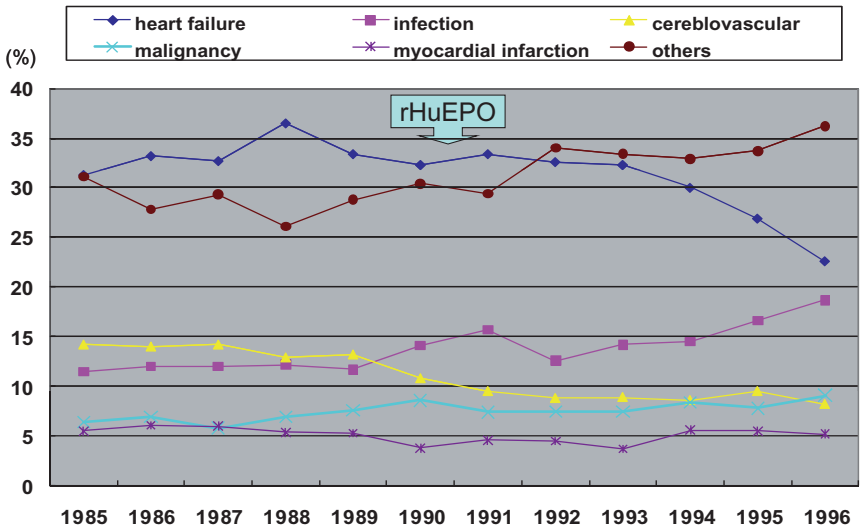
In Japan, although the target Hb levels for CKD patients in clinical studies on novel ESAs had been set at 11–13 g/dL, it needed to be reset because the Ministry of Health, Labor and Welfare changed the contents of its guidance with the upper limit of Hb level lowered to 12 g/dL based on the FDA recommendation.

In a long-term comparative study completed before the FDA recommendation, no safety problem arose in the high Hb group (target Hb 11–13 g/dL) using darbepoetin alfa (DA) compared with the low Hb group (target Hb 9–11 g/dL) using rHuEPO and the quality of life (QOL) and cardiac function were better than those in the low Hb group (14). The 2008 JSDT guidelines recommended a target Hb level of 11 g/dL or greater in CKD patients, and dose reduction or interruption should be considered if the Hb level exceeds 13 g/dL. For patients with severe CVD or other considerable diseases, the upper limit was recommended as 12 g/dL.

After the revisions of the Western and the Japanese guidelines described above, the results of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) were published (15). This study was the first placebo-controlled DA double-blind randomized controlled trial (RCT) performed on 4038 patients with type 2 diabetes and Hb level of not more than 11.0 g/dL and eGFR at 20–60 mL/min/1.73 m^2. The primary endpoints were the time to the composite outcome of death and cardiovascular disease, death and end-stage renal disease. In 46% of patients in the placebo group whose Hb level dropped down less than 9 g/dL, DA was administered as rescue therapy in accordance with the protocol and the median Hb in the course was maintained at 10.6 g/dL. About 30% of patients in both groups demonstrated onset of primary end points during the course of treatment but the difference between the two groups was not significant. However, fatal or non-fatal stroke was more likely to occur in the patients assigned to DA (hazard ratio 1.92: $P < 0.001$). Although there was no significant difference in systolic blood pressure between the two groups, diastolic blood pressure was significantly higher in the patients assigned to DA than those assigned to placebo. In the CHOIR study, no differences in the incidence of stroke were found between the groups which had different Hb levels. It was assumed that the difference in diastolic blood pressure might be involved in the large number of strokes in the DA group in the TREAT study.

Malignancy other than skin cancer was an exclusion criterion in the TREAT, however 188 patients in the DA group and 160 in the placebo group had a history of cancer. Fourteen patients in the DA group and one in the placebo group died of cancer. There were significantly more cases in the DA group.

Surprisingly, red-cell transfusions were received by 496 patients (24.5%) in the placebo group during the follow-up period of 29.1 months (median), and even in the DA group, though significantly fewer, 297 patients (14.8%) received red-cell transfusions. This



Modified from: An Overview of Dialysis in Japan (as of Dec. 31 1996) by JSDT

FIG. 1. Annual transition of causes of death in hemodialysis patients before and after launching of recombinant human erythropoietin (rHuEPO) in 1990 in Japan.

high frequency of transfusions thus shown is hard to believe for Japanese nephrologists.

The TREAT study concluded that this risk outweighed the potential benefits for many persons involved in clinical decision-making. The TREAT study raised disturbing questions for nephrologists worldwide. In Japan, the Japanese Society of Nephrology (JSN) started to study the effects of rHuEPO on stroke and cancer, and performed a questionnaire survey to CKD patients. The results will be presented at the annual meeting of the JSN this year. Indeed, we reported that no significant relation between the use of rHuEPO and stroke or deterioration of cancer were found on 549 patients (289 using rHuEPO). In our study, the rate of patients with history of CVD or cancer was extremely low compared with the subjects in the TREAT study. Moreover, patients did not receive any blood transfusions during the 6-month survey period. So far, no epidemiological surveys showing increases in cancer deaths after the treatment with ESAs have been reported. In Japan, the results of an annual statistical survey on dialysis patients performed by the JSDT did not reveal any trend for an increase in cancer deaths after 1990 when rHuEPO became available for dialysis patients, and what is more, the percentage of deaths due to stroke has decreased since 1990 (Fig. 1).

These differences are clearly caused by markedly different characteristics of HD population in Japan and those in the TREAT and CHOIR studies as shown in Table 1. The major factor producing the differences would be the medical systems in Japan and in the US. In Japan, almost every person is provided with annual health checkups and the medical costs are much lower than in the US. Indeed, the high rate of discovery of CKD without symptomatic complications was reported in Japan compared with the US. The CKD patients may be treated earlier in Japan. In the US, few patients with no symptoms might visit their medical institutions because of the high medical costs, and when symptomatic disease appears, people would then be tested and diagnosed with CKD.

The JSDT 2008 guidelines working group carefully analyzed the results of the CHOIR study and the secondary analysis and set the upper limit of Hb level to be 12 g/dL in patients with severe CVD or patients considered as high risk by attending physicians.

In the subgroup analysis of the TREAT study, the incidence of CVD was significantly higher in the DA group than in the placebo group in patients with a history of stroke, but not without the history (Fig. 2), which would support the lower target Hb level for patients with a history of CVD event in the JSDT guidelines (16).

Detailed information about the TREAT study is still limited. We need to reconsider the significance of treatment using ESAs, however it seems difficult to come to any conclusion from the present findings so far. The lessons from the results of the CHOIR and TREAT studies are that high risk patients should be treated with a lower Hb target.

In the guidelines for treatment of hypertension, the finely targeted blood pressure levels and the antihypertensive agents were set based on age and complications. Likewise, more detailed specifications for treatment of renal anemia are probably needed.

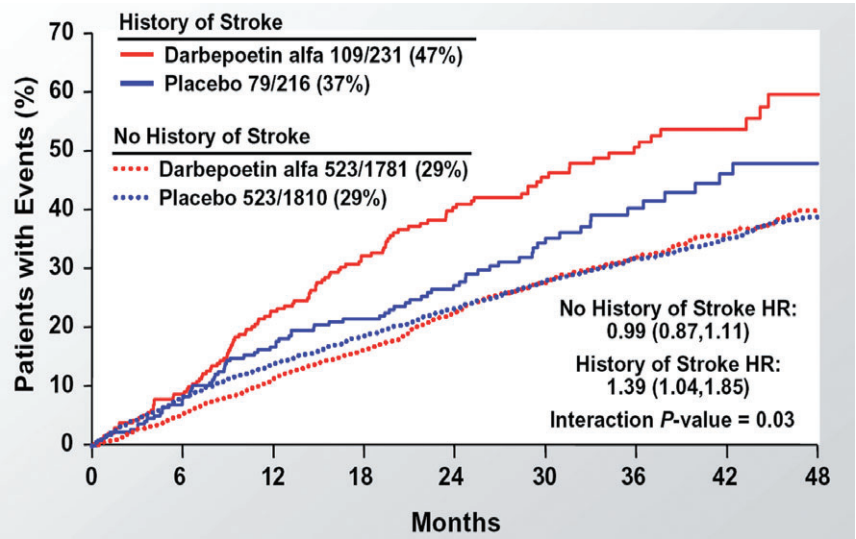


FIG. 2. Kaplan-Meier estimates of the probability of cardiovascular composite events in patients with or without history of stroke in TREAT study.

From this viewpoint, the Japanese guidelines might be valuable in terms of separate target Hb levels for HD and CKD patients and the description of previous CVD or evaluations by attending physicians on the specifications of setting target levels.

In the current status of rHuEPO treatment of CKD patients in Japan, however, most patients did not reach the target levels mainly because of the limited dose of rHuEPO.

If long-acting ESAs become available in the future and nephrologists come to pay more attention to renal anemia, the prognosis and QOL in CKD and HD patients would be improved.

In conclusion, we should consider possible measures for tailor-made control of Hb to target levels for each individual CKD patient, whose ages and genders are different, and also to meet medical needs for the patients who have a diverse range of underlying diseases and complications. Randomized controlled trials will undoubtedly be necessary in the very near future in Japan.

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