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Idarucizumab for Dabigatran Reversal-full Cohort Analysis (RE-VERSE AD Study)

Dabigatranın Etkisinin Tersine Çevrilmesi için İdarucizumab-Tüm Kohort Analizi (RE-VERSE AD Çalışması)

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Currently, patients who take oral anticoagulant medication for the treatment of thrombosis or prophylaxis can benefit from anticoagulant reversal medications when they have a life-threatening bleed or they need an urgent surgical intervention. Idarucizumab is a humanized monoclonal antibody, which has high affinity and specificity to dabigatran and rapidly reverses its anticoagulant effect by binding to it (1).

A multi-center, prospective and open-label trial was designed to investigate the reversal of the anticoagulant effect of dabigatran by idarucizumab by administering it to 2 groups of patients with a dose of 5 g, intravenously (2). In this trial, group A consisted of patients with uncontrolled and life-threatening bleeding and group B comprised patients who should be treated with emergency interventions within 8 hours following restoration of normal homeostasis (3). The primary endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab. This was determined by the diluted thrombin time or ecarin clotting time, which show a linear relation with the level of dabigatran. Secondary endpoints included the restoration of hemostasis and safety measures.

Five hundred three patients, 301 of whom constituted group A and 202 comprised group B, from 173 centers were included in the trial. Of these patients, more than 95% were using dabigatran to be protected against stroke due to atrial fibrillation. According to patients' statement, the time interval between the last uptake of dabigatran and the first idarucizumab infusion was 15 hours in group A and 18 hours in group B. The maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab was 100% [95% confidence interval (CI): 100-100] on the basis of the diluted thrombin time or ecarin clotting time. Also, it was shown that the percentage reversal of the anticoagulant effect was independent of age, sex, kidney functions, and the level of dabigatran at initiation. The level of dabigatran at initiation was 110 ng/mL in group A and 74 ng/mL in group B, and it was measured 10 ng/mL or lower following administration of idarucizumab in patients in whom the level of idarucizumab was re-measured. The level of idarucizumab was still low after 24 hours in most of patients, but it was higher than 20 ng/mL in 23% of patients. Recurrent or continuing bleeding in 10 patients in group A with dabigatran levels higher than 20 ng/mL were thought to be related with the level of dabigatran and an additional 5 g idarucizumab was administered to 3 patients.

Of the patients in group A, 137 (45.5%) were admitted with gastrointestinal bleeding and 98 (32.6%) had intracerebral hemorrhage. When 98 patients for whom the time of cessation of bleeding was not known were excluded from group A; it was shown that bleeding stopped within 24 hours in 67.7% of the remaining patients and the median cessation time was 2.5 hours (95% CI: 2.2-3.9). The median time was 1.6 hours in group B until the initiation of surgical intervention and the homeostasis during

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intervention was found to be normal in 93%, mildly abnormal in 5.1%, and moderately abnormal in 1.5% of the patients. Antithrombotic treatment was re-initiated in 22.9% of the patients in group A and 66.8% of the patients in group B, 72 hours after the administration of idarucizumab.

The rate of development of thrombotic events in group A was 6.8% and 7.4% in group B at the 90th day. The mortality rates were 18.8% and 18.9%, respectively. Severe adverse events developed within 5 days following idarucizumab administration in 66 patients (21.9%) in group A and 51 patients (25.2%) in group B. On the other hand, most of these adverse events were index events or were related with concomitant conditions. Hence, there were no serious adverse safety signals.

As a result, idarucizumab rapidly and completely reverses the anticoagulant effect of dabigatran in more than 98% of patients who have uncontrolled bleeding or need an emergency surgical intervention; it is very effective in this group of patients.

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