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Two new drugs in the treatment of Multiple Sclerosis: BG-12 and Alemtuzumab

Two new phase III studies for the treatment of multiple sclerosis (MS) that have been under way for a long time were published last year. The first one of these is a molecule called BG-12 (dimethyl fumarate). Originally being used for the treatment of psoriasis since 1950's, the success achieved with this drug in MS patients in the 2008 phase II study triggered the planning of 2 phase III trials.

In the first one of these trials named DEFINE, two different doses of 240 mg BG-12, twice or three times a day, were compared to placebo. After two years, both of these doses were found to be superior to placebo at the primary and secondary termination points. Placebo group showed relapse at a rate of 46%, low-dose (480 mg/day) group showed relapse at a rate of 27%, and the high-dose group (720 mg/day) at 26%. The annual relapse speeds were found to be 0.17 for the low-dose group, 0.19 for the high-dose group and 0.36 for the placebo group. These results suggest that the treatment reduced the annual relapse speed by half. Additionally, the drug provides carries a risk of permanent debilitation at 38% in the low dose and 34% at the high dose relative to the placebo. The radiological measures such as the number of contrast defined lesions and new T2 lesion load also seem to be favorable for the treatment groups.

In the CONFIRM study, two doses of BG-12 were compared to placebo and glatiramer acetate. In this study, both doses of BG-12 replicated the results in the DEFINE study as compared to the placebo group. Even though the study lacked the necessary power to fully compare glatiramer acetate and BG-12, it is worth noting that the annual relapse speed, the number of new T2 and T1 lesions show a more favorable trend for BG-12.

There has been over 30.000 patient year of experience on the effects of fumaric acid esters in psoriasis patients. Based on those, it is safe to see that BG-12 is a relatively safe drug with rare adverse effects. Furthermore, no serious drug side effects such as cancer or opportunistic infections were observed in either DEFINE or CONFIRM studies. However, rashes, diarrhea, stomach pain, nausea, temporary liver function test anomalies or lymphopenia were commonly seen.

Another novel treatment that stood out last year for the treatment MS was alemtuzumab. As an anti-CD52 monoclonal antibody, this molecule provides permanent decrease in T and B lymphocyte populations.

In CARE MS I study, 563 patients who have not received treatment before were given 12 mg/day IV alemtuzumab or interferon beta-1a µg SC 3 times per week. Alemtuzumab treatment was given for 5 days at the study onset and 3 days after the 12th month. After two years, the interferon group showed relapse with 40% and alemtuzumab group showed relapse at 22% (relative risk reduction: 55%, $p<0.0001$). In the interferon group, 11% of the patients showed permanent debilitation while it was only 8% in the alemtuzumab group (hazard rate 0.7). The striking results acquired in this study conducted against an active medicine sadly showed some adverse effects as well. These include serious infusion reactions at 3%, thyroid gland dysfunction, infections and thrombocytopenia that developed in 3 patients. In addition, 2 patients developed thyroid papillary carcinoma.

In the CARE MS II study, 628 patients who had at least one attack despite interferon or glatiramer use were included. In this trial, it was planned that the patients would be randomly divided in three groups as interferon beta-1a, alemtuzumab 12 mg/day and 24 mg/day groups. However, due to the difficulties in patient recruitment, 24 mg/day alemtuzumab group was taken out of the study. After 24 months, 51% of the interferon group showed relapse, while only 33% showed relapse in the alemtuzumab grou (relative risk reduction 49%, $p<0.0001$). In the permanent cumulative debilitation ratio, alemtuzumab seemed more favorable with a 42% reduction (20% versus 13%, hazard rate 9.58, $p=0.008$). In this study, 1% of the patients also developed immune thrombocytopenia.

The superiority in the convenience of use for orally administered BG-12 and alemtuzumab which is administered only for a short duration in a year is undisputed compared to other forms of treatment. BG-12's adverse effect profile is extremely tame while

that of alemtuzumab's is more concerning in comparison. This difference suggests that more patient experience may be required before alemtuzumab becomes available for general use.

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A New Coagulant for Atrial Fibrillation: Apixaban

As an unrivaled choice for atrial fibrillation, warfarin decreases the risk of stroke or systemic embolism by 40% compared to asprin. In the last 2 years, apixaban also began its clinical trials in addition to a thrombin inhibitor called dabigatran and a factor-X inhibitor called rivaroxaban as alternatives to warfarin.

In the ROCKET AF study where warfarin was pitted against rivaroxaban and in the RE-LY study where dabigatran was pitted against warfarin in atrial fibrillation patients, these drugs were found to decrease the risk of embolism and hemorrhagic complications compared to warfarin. In the OVERROES study published in 2011 using the drug called apixaban of this group, which provided anticoagulation through factor Xa inhibition, atrial fibrillation patients who are not using warfarin were randomized as aspirin and apixaban groups. The study was terminated earlier than planned because of the clear superiority of apixaban's results. In this study, in addition to apixaban's significant protective effect against stroke or systemic embolism, it was also seen that the risk for major hemorrhage and intracranial bleeding were also not increased.

In the ARISTOTLE study planned as a follow-up for OVERROES, 18201 atrial fibrillation patients who are under risk for at least one stroke were randomized into two groups as the apixaban group using 5mg twice a day and the warfarin group using enough dosage to keep the INR level at 2.0-3.0. The primary termination points were stroke and systemic embolism. In the apixaban group, annually 1.3% of the patients reached the primary termination point whereas in warfarin group this rate was 1.6% (hazard ratio 0.79. CI 0.66-0.95; p<0.001 for noninferiority, p=0.01 for superiority). Major bleeding was seen in the 2.1% of the apixaban group whereas it was 3.1% of the warfarin group. The mortality rate in the apixaban group was also smaller. Hemorrhagic stroke ratio was also reduced almost by half in the apixaban group compared to warfarin group.

ARISTOTLE's subgroup analyses were published last year. The data was divided in half according to the presence or absence of stroke or transient ischemic attack. In 3436 patients with previous history of stroke, the stroke or systemic embolism rate seen in 100 combined patient years was 2.5% for the apixaban group whereas it was 3.2% for the warfarin group (hazard ratio 0.76, 95% CI 9.56 to 1.03). I patients who doesn't have previous history of stroke, however, this rate was 1.0% for apixaban and 1.2% for warfarin. These findings suggest that the drug is more effective in people with a previous history of stroke or transient ischemic attacks.

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The Use of Rituximab in Myasthenia Gravis with MuSK Antibody

Even though the evidence suggesting the benefit of rituximab in myasthenia gravis (MG) is still at an anecdotal level, the trend suggests that this may indeed be true. Myasthenia gravis with muscle-specific kinase (MuSK) antibody patients progress worse than those with MG with acetylcholine receptor (AchR) antibody. The studies using rituximab reported improvement in 81-96% of the treatment resistant MG patients. However, due to the fact that the follow-up period of these studies were around 1.5 years, the long-term effects of the drug still remain unknown. Diaz-Manera et al.'s study that was published in Neurology last year reduces this mystery to some extent.

Seventeen treatment resistant MG patients were included in this study. The authors defined treatment resistance as the lack of control on the disease progress despite the use of prednisone and at least three different immunosuppressants. Rituximab treatment was administered with 375 mg/m2 per weed for 4 weeks and once a month in the following two months. Dose repetition was only administered only when the myasthenic symptoms were severe enough to interfere with daily activities.

Fifteen of the patients included in the study were women with the mean age of 44. Six of the patients were positive for MuSK and 11 were positive for AchR antibodies. Ten AchR-positive patients that were followed for 31 months showed clinical improvements while 6 of them needed re-infusion. However, 4 of the MuSK-positive patients showed full remission and 2 showed only mild residual symptoms at the end of the treatment. In addition, it was possible to lower prednisone's dose and to cease the immunosuppressive treatments in the MuSK-positive patients. It

is worth noting that the antibody levels in half of these MuSK-positive patients turned negative and reduced by half compared to the basal level in the rest of the patients.

Even though rituximab treatment is generally well-tolerated, it is possible to observe mild allergic reactions such as facial redness and rashes. This condition can easily be taken under control with parenteral steroids and antihistamines.

Although the literature shows PML cases with a rate of 1/25.000, none of these were MG patients. In this study where the observed side effects were tolerable, 16 out of 17 patients showed clinical improvement while the most benefit was seen in the MuSK-positive patients.

The change in the rituximab response depending on the antibody type may be related to the increased role of IgG1 and IgG3 in AchR MG while IgG4 is more important for MuSK IgG4. This study suggests that rituximab can be a viable early treatment strategy for steroid resistant Musk positive MG cases.

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