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Andexanet Better Controls Hematoma Expansion Than Usual Care In Patients with Intracerebral Hemorrhage who receive Factor Xa Inhibitors

Date: May 15, 2024

Patients receiving factor Xa inhibitors are at risk of acute intracerebral hemorrhage, which can lead to hematoma expansion. Andexanet alfa, a reversal agent for factor Xa inhibitors, was studied for its efficacy and safety in controlling hematoma expansion.

This randomized trial compared andexanet with usual care in patients with acute ICH with hematoma expansion volume of 0.5 to 60ml and had taken factor Xa inhibitors within 15 hours before hemorrhage onset. Patients were randomly assigned in 1:1 ratio to receive andexanet, high- or low-dose bolts over 15 to 30 minutes followed by continuous infusion over 2 hours, or usual care which could include prothrombin complex concentrate. The primary endpoint was hemostatic efficacy, defined as hematoma expansion of 35% or less at 12 hours, an increase in the score on the National Institute of Health Stroke Scale of less than 7 points (scores range from 0 to 42, with higher scores indicating worse neurologic deficit) at 12 hours, and no receipt of rescue therapy between 3 hours and 12 hours. Safety endpoints included thrombotic events and death.

A total of 530 patients were enrolled, with 263 receiving andexanet and 267 receiving usual care. Of the patients relieve usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 67.0% (n=150) of the andexanet group compared to 53.1% (n=121) the usual care group (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). Thrombotic events occurred in 10.3% (n=27) of the andexanet group versus 5.6% (n=15) in the usual care group (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively.

In conclusion, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke.

Source: www.nejm.org

Dupilumab Reduces Exacerbations in COPD Patients with Type 2 Inflammation

Date: May 20, 2024

Dupilumab, a fully human monoclonal antibody that is used in treating chronic obstructive pulmonary disease (COPD) with type 2 inflammation. Dupilumab targets interleukin-4 and interleukin-13, crucial drivers of this inflammation. In a previous phase 3 trial, Dupilumab was effective in reducing exacerbations and showed results in improvements of lung function and patient-reported health-related quality of life. The NOTUS study was conducted to confirm efficacy and safety findings.

In this double-blind, randomized, placebo-controlled phase 3 trial, 935 patients with COPD and elevated blood eosinophil counts (≥300 cells/μl) were enrolled. Participants received either 300 mg of dupilumab or a placebo every 2 weeks. The study aimed to evaluate the annualized rate of moderate or severe exacerbations, alongside secondary measures like lung function (FEV1) at weeks 12 and 52, and quality of life (SGRQ scores) at week 52.

Among 935 patients who underwent randomization, 470 were assigned to the Dupilumab group and 465 to the placebo group. Results revealed a significant reduction in the annualized rate of moderate or severity exacerbation for the dupilumab group (0.86, 95% confidence interval [CI], 0.70 to 1.06) compared to placebo (1.30, 95% CI, 1.05 to 1.60), with a rate ratio of 0.66 (95% CI, 0.54 to 0.82; P<0.001). Improvements in FEV1 were noted at both 12 and 52 weeks in the dupilumab group as compared to the placebo group, with a significant least-squares mean difference at week 12 of 82 ml (P<0.001) and at week 52 of 62 ml (P=0.02). No significant difference was found in SGRQ scores from baseline to 52 weeks. Adverse events were similar across both groups, consistent with the established profile of dupilumab.

In conclusion, dupilumab effectively reduced exacerbations and improved lung function in COPD patients with type 2 inflammation as indicated by elevated blood eosinophil counts.

Source: www.nejm.org

Reteplase Noninferior to Alteplase for Patients with Acute Ischemic Stroke

Date: June 14, 2024

Intravenous alteplase is the standard thrombolytic agent used for acute ischemic stroke within 4.5 hours after symptom onset. Reteplase is a recombinant plasminogen activator that is characterised by a double-bolus approach with a fixed dose regimen. The RAISE trial was conducted to study the efficacy and safety of reteplase as compared with alteplase as an alternative thrombolytic agent in patients with acute ischemic stroke.

In this phase 3, prospective, open-label, noninferiority, randomized trial conducted at 62 sites in China, patients with ischemic stroke within 4.5 hours after symptom onset were randomly assigned in a 1:1 ratio to receive intravenous reteplase (a bolus of 18mg followed by a second bolus of 18mg 30 minutes later) or intravenous alteplase (0.9mg/kg of body weight; maximum dose of 90mg). The primary efficacy outcome was an excellent functional outcome, defined as a score of 0 or 1 on the modified Rankin scale (ranges from 0 to 6) at 90 days. The primary safety outcome was symptomatic intracranial hemorrhage within 36 hours after symptom onset.

A total of 707 and 705 patients were assigned to the reteplase and alteplase group, respectively. The primary efficacy outcome occurred in 79.5% of the patients in the reteplase group and in 70.4% of the patients in the alteplase group (risk ratio, 1.13; 95% confidence interval [CI], 1.05 to 1.21; P<0.001 for noninferiority and P=0.002 for superiority). Symptomatic intracranial hemorrhage within 36 hours after disease onset was observed in 2.4% (n=17) and 2.0% (n=14) of the patients in the reteplase and alteplase group, respectively (risk ratio, 1.21; 95% CI, 0.54 to 2.75). However, the incidence of any intracranial hemorrhage at 90 days was higher with reteplase than with alteplase (7.7% vs. 4.9%; risk ratio, 1.59; 95% CI, 1.00 to 2.51), as was the incidence of adverse events (91.6% vs. 82.4%; risk ratio, 1.11; 95% CI, 1.03 to 1.20).

In conclusion, patients with acute ischemic stroke who were eligible for intravenous thrombolytic therapy within 4.5 hours after symptom onset, reteplase was superior to alteplase with respect to an excellent functional outcome at 90 days. However, patients who received reteplase was associated with a higher incidence of any intracranial hemorrhage.

Source: www.nejm.org

Regulatory Updates of Medical Gases as Pharmaceutical Products in Hong Kong

Date: June 17, 2024

The Pharmacy and Poisons Board of Hong Kong (the Board) has recently endorsed the regulation of medical gases as pharmaceutical products under the Pharmacy and Poisons Ordinance (Cap. 138) (the Ordinance) with effect from June 14, 2026.

Considering the regulatory control of medical gases in other jurisdictions and the current local situation, the Board agreed that medical gases should be regulated as pharmaceutical products in September 2023. The final decision regarding the issue was made under the overall support from the general public and relevant stakeholders, according to the Board's meeting on June 14, 2024.

A preparatory period of two years (i.e. from June 14, 2024, to June 13, 2026) is given for the trade to apply for relevant licences and product registration. In this regard, medical gases must be registered with the Board before they can be legally sold and supplied in Hong Kong when the new regulatory control comes into effect. Traders of medical gases must also obtain relevant license(s) from the Board before conducting manufacture, wholesale (including import and export) of pharmaceutical products and retail sales of pharmaceutical products containing poisons.

Under the Ordinance, illegal possession or sale of unregistered pharmaceutical products or prescription drugs, and manufacture, wholesale of pharmaceutical products and retail sales of pharmaceutical products containing poisons without relevant licences are criminal offences. The maximal penalty upon conviction is a fine of $100,000 Hong Kong dollars and two years' imprisonment for each offence.

Source: www.drugoffice.gov.hk

Weekly Subcutaneous Semaglutide Reduces the Risk of Major Kidney Events in Patients with Type 2 Diabetes and Chronic Kidney Disease

Date: July 11, 2024

Type 2 diabetes (T2DM) has been recognized as one of the common causes for chronic kidney disease that underlies various kidney and cardiovascular disease events. Renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and finerenone are the guideline-recommended treatment options for chronic kidney disease in patients with T2DM with proven renal and cardiovascular protective effects. Semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, is currently indicated for treating T2DM and providing long-term weight management whereas its effect on preserving renal function in T2DM patients is currently under investigation.

The FLOW trial was an international, double-blind, randomized, placebo-controlled trial that involved 3533 type 2 diabetes patients with defined chronic kidney disease (i.e. estimated glomerular filtration rate [eGFR] between 25 to 75 ml/min/1.73m^2). Participants were then randomized in 1:1 ratio to receive weekly subcutaneous injections of semaglutide 1mg over an 8-week dose-escalation regimen (n=1767) or placebo (n=1766). Primary outcomes of the study include the onset of major kidney disease events, sustained reduction of eGFR of ≥50% from baseline or death from kidney-related or cardiovascular causes. Safety outcome of the trial was also assessed based on data regarding serious adverse events and any events leading to treatment discontinuation.

Major kidney disease events were found less frequent in the semaglutide group than the control group (hazard ratio=0.76; 95% confidence interval [CI], 0.66-0.88; P=0.0003), and the results were consistent across prespecified patient subgroups. The risk of major related cardiovascular events was observed to be statistically lower in patients taking weekly subcutaneous semaglutide (212 vs. 254 events; hazard ratio=0.82; 95% confidence interval [CI], 0.68-0.98; P=0.029). Fewer serious adverse events related to infections or serious cardiovascular disorders were reported in the semaglutide group (49.6%) then placebo (53.8%).

Weekly subcutaneous semaglutide reduces the risk of developing clinically significant kidney and cardiovascular outcomes in patients with T2DM and chronic kidney disease based on the current findings in the FLOW trial.

Source: www.nejm.org

Insignificant Risk Reduction for Symptomatic SARS-CoV-2 Infection using Oral Nirmatrelvir-Ritonavir as Post-exposure Prophylaxis

Date: July 18, 2024

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection still remains as an ongoing threat towards the local healthcare system and the global community. Previous real-world modelling also suggested that nearly half of the disease transmission occur before symptom onset, especially with the emergence of the B.1.617.2 (delta) and B.1.1.529 (omicron) variants. Nirmatrelvir-ritonavir has been approved for treating mild-to-moderate SARS-CoV-2 infection in adult patients at high risk to progress to severe complications. Yet, its effect as post-exposure prophylaxis among household contacts of infected persons remains uncertain.

In this phase 2-3, double-blind, randomized and placebo-controlled trial, a total of 2957 adult participants with negative screening rapid antigen test for SARS-CoV-2 at baseline were randomized in 1:1:1 ratio to receive oral 300mg nirmatrelvir and 100mg ritonavir daily for 5 days (n=921), 10 days (n=917) or matching placebo (n=898). The 5-day nirmatrelvir-ritonavir group are expected to take 5-days of matching placebo upon completion of their respective 5-day nirmatrelvir-ritonavir regimen. Primary efficacy of the trial was analyzed based on the development of symptomatic SARS-CoV-2 infection to be confirmed by reverse-transcriptase-polymerase-chain-reaction (RT-PCR) or rapid antigen screening on Day 14. The safety outcomes of the prophylactic nirmatrelvir-ritonavir regimen were also assessed towards the end of the study period.

The incidence of symptomatic, confirmed SARS-CoV-2 infection by Day 14 of the trial did not demonstrate statistically significant differences between each nirmatrelvir-ritonavir group and placebo in general. Corresponding risk reductions compared with placebo were 29.8% (95% confidence interval [CI], -16.7-57.8; P=0.17) 35.5% (95% confidence interval [CI], -11.5-62.7; P=0.12) in the 5-day and 10-day treatment arm respectively. No remarkable differences in developing symptomatic COVID-19 infection were noted among participants at high risk for progression to severe complications as well. Reports of adverse reports were similar in both 5-day and 10-day treatment groups, with dysgeusia being the most frequently reported adverse event.

To summarize, post-exposure prophylactic doses of nirnatrelvir-ritonavir did not provide significant risk reduction for adult household contacts of symptomatic COVID-19 patients to develop SAR-CoV-2 infection as compared with placebo.

Source: www.nejm.org