Review of Selected Contemporary Treatments for Ischemic Stroke

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Abstract

Stroke is considered a serious medical emergency, and it is crucial to get immediate medical treatment. Early detection can limit brain damage and complications. Ischemic stroke (IS) is caused by atherosclerosis, which is the hardening of the arteries. The accumulation of fats and cholesterol on the wall of an artery causes narrowing that eventually leads to blockage or interruption of blood flow through that artery, thus reducing blood flow to tissues and organ perfusion. A reduction or a blockage in blood flow to the brain can cause neurological problems such as stroke or ischemic stroke. This review critically analyzes the safety and effectiveness of novel treatments for ischemic stroke. The literature search was conducted via PubMed and Google Scholar. Review articles show that statin therapy helps in preventing additional strokes from occurring in patients that had small-vessel occlusion, large-artery atherosclerosis, and strokes that are caused by multiple reasons. Results showed that high dosages of simvastatin proved to be the most effective treatment in improving stroke prognosis and ineffective in preventing mortality. Mesenchymal stem cell (MSC) therapy might also help by improving the damaged tissue of IS through various mechanisms, but research still needs to be done on the neurogenesis and angiogenesis pathways. MSC was successful in clinical use, but it still needs to be conducted in a large sample size. Focusing on the effectiveness of the safety of MSC and the timing and optimal dosage are the main challenges in its clinical use and need to be conducted before taking it into clinical trials. Monoclonal antibody (mAb) therapy showed a positive benefit in increasing the neuronal repair, and regeneration in the brain of the animal models. Further research needs to be done on human stroke patients in assessing the benefit of mAb therapy.

Introduction

Stroke is defined as a sudden loss of brain function that occurs due to the interruption of blood flow to the brain. This causes the brain cells in the affected area to die (1). Stroke is the third leading cause of death, and it is also the leading cause of disability in the United States. Each year, 15 million people suffer from stroke worldwide (2). There are three types of strokes, which include: hemorrhagic (ICH), transient ischemic attack (TIA), and ischemic stroke (IS). ICH occurs when a blood vessel is ruptured, causing bleeding inside the brain. TIA, also known as a mini stroke, causes a disruption of blood flow to the brain for a short period of time. Having an episode of TIA indicates that it is more likely someone will have a stroke in the future. IS takes place when there is a blockage in an artery that causes a blood clot. Blood flow is being stopped from traveling to different parts of the brain, and that portion of the brain will become deprived of oxygen (1).

Ischemic stroke is the most common type among the three and accounts for 87% of all strokes (2). While a stroke can affect people of all ages, the elderly are more susceptible. As an individual's age increases the arteries steadily begin to narrow and develop plaque (3). Also at risk are individuals who have underlying health problems such as diabetes, high blood pressure, and high cholesterol (4). Individuals who show symptoms of stroke might experience a sudden loss of strength or numbness in the arms or legs. They can also have severe and unusual headaches, dizziness, and difficulty speaking (5). Though strokes have many underlying risk factors and symptoms, strokes can be prevented and treated. Detecting and receiving treatment for IS early reduces the risk of having permanent brain damage. The sooner the signs and symptoms of a stroke are diagnosed, the more effective the potential treatment will be.

This review focuses on ischemic stroke, the most common type of stroke which typically has a better chance of survival. If left untreated, IS can then lead to hemorrhagic strokes, which are the deadliest and are highly difficult to treat (6). It is important to know about stroke and the effects it can have on the individual's life and family. Educating people on the risk factors of developing stroke can help individuals to take precautions that can save many lives and reduce the number of cases per year. Having new treatments in combination with current treatments can help treat IS faster and better. A literature review was conducted to determine which of the novel treatments — statin therapy, mesenchymal stem cell therapy, or monoclonal antibody therapy — is most effective for slowing and treating ischemic stroke.

Methods

A literature review of review and primary articles were conducted using electronic databases such as Google Scholar and PubMed to retrieve studies on novel treatments for ischemic stroke published between 2018 and 2020. Terms such as "ischemic stroke," "current treatments," "new treatments," "novel treatments," "emerging treatments," and "upcoming treatments" were used to find the articles. Articles were selected according to the following eligibility criteria: randomized control trial, clinical trial, peer-reviewed, systematic review, meta-analysis, free full text, general geographical location, English language. Only articles that addressed current and new treatments for ischemic stroke were reviewed. Articles that were published in 2017 and earlier were excluded, as were articles that did not include or address the terms ischemic stroke and treatments. The first search produced 25,800 total articles from both Google Scholar and PubMed. After excluding articles that were not relevant to the topic, 3,555 remained for full-text reviewed articles. The articles were narrowed down to

25 using the inclusion and exclusion criteria. Ten articles were selected for final analysis.

Results

The use of statin therapy in the treatment of ischemic stroke

High-level serum cholesterol leads to a buildup of fatty particles in the arteries. When the arteries are blocked, it can increase the risk of cardiovascular disease and stroke. Statins are drugs that can help remove plaque from arteries. Statins are prescribed by doctors to help reduce cholesterol levels and help prevent patients from having a stroke or heart attack (7). Statins have been shown to be highly effective in reducing the risk of cardiovascular disease (CVD) up to 10% in primary prevention and 5% in secondary prevention (8). Statins help reduce the risk of CVD and prevent the onset of the disease (primary prevention). They are also effective in slowing the progression of CVD, which in turn reduces the risk of morbidity and mortality. Based on the CVD benefit, the use of statin drugs is being expanded to the treatment of other diseases.

Since statins are important in helping stroke patients, it has become a vital breakthrough in stroke prevention. Clinical trials have shown positive results in analyzing the safety and effectiveness of statin treatment, which leads to using statin treatment more often on stroke patients (9). In addition to clinical trials, cohort studies have been conducted to help in understanding how the treatments can be used in everyday clinical practice (9). The authors Vitturi and Gagliardi conducted a prospective cohort study of patients who were diagnosed with ischemic stroke. Participants who were 18 years and older and had their first ischemic stroke were included. They excluded participants that were followed up less than 24 months and using other lipid-lowering drugs. Participants were grouped into four different categories: non-statin, simvastatin 20 mg per day, simvastatin 40 mg per day, and high-potency statin groups (atorvastatin 40 mg per day or rosuvastatin 10 mg per day). The high-potency statin groups were those groups that were given atorvastatin 40 mg per day or rosuvastatin 10 mg per day that was expected to reduce the LDL cholesterol level by more than 50%. Participants were followed up by phone interviews for 2 years or until they died. Patients that were excluded based on their death were determined through searches from the National Registry of Death to detect (9).

The primary outcome was the post-stroke functional limitations, which were assessed using the modified Rankin scale (mRS). After the IS participant was admitted to the hospital, each of their post-stroke functional limitations was assessed during days 7, 30, 6 months, and 2 years. Participants who had an mRS score ≥3 were defined as unfavorable outcomes, while an mRS score ≤2 was considered a favorable outcome. Secondary outcomes were those participants that had recurrent strokes such as hemorrhagic or ischemic stroke, any major cardiovascular disease, and cause of mortality. The results showed no significant difference in NIH Stroke Scale/Score (NIHSS), atrial fibrillation, smoking, dyslipidemia, etc. Patients who were given a statin had a lower risk of developing CVD (OR=0.3; 0.1-0.7; p=0.01) (9). There were not any differences found in the mortality rate of using the statin drug (OR=0.6; 0.1–2.3; p=0.73) (9). Three hundred and seven participants had a favorable functional outcome with a medium mRS score of 2. Results also showed that taking a statin at an early stage of IS resulted in a favorable neurofunctional outcome and appeared to prevent recurrence of stroke ($p < 0.01$). Participants who terminated their treatment or did not fully respond to the treatments had poorer functional outcomes and were more likely to have another stroke ($p < 0.01$). Participants who did not receive the statin drug had a higher risk of a second stroke and worse functional outcomes ($p < 0.01$).

Based on the secondary prevention description of their study, statin therapy was more beneficial to those participants that were given the simvastatin 40 mg than those that were given the simvastatin 20 mg and high-intensity statin. Overall, patients that received the simvastatin 40 mg and the high-intensity drug had the best functional recovery in a year after they had a stroke ($p < 0.05$) (9). Statin therapy was also successful in preventing another stroke from occurring in patients that had small-vessel occlusion, large-artery atherosclerosis, and strokes caused by multiple reasons (9). In summary, statin use was associated with a significant beneficial effect in patients with ischemic stroke such as reducing the risk of stroke recurrence and having better functional outcomes. Without the use of statin, patients did not see any change in their functional outcomes (9, 16).

Mesenchymal stem cells (MSC) and their potential for neuroregeneration in ischemic stroke

Mesenchymal stem cells help in repairing different disorders and diseases such as kidney, neurodegenerative, autoimmune diseases, and graft-versus-host diseases. They help replace damaged cells and wound remodeling (10). Mesenchymal stem cells (MSC) are cells that are found in the bone marrow that are important in making and repairing the tissues in bones and cartilage. MSC is considered a novel therapeutic agent in treating diseases and injuries because it helps in the process of self-renewal of tissues and can benefit in healing cells (11).

MSC works by expressing a variety of cytokines and chemokines that help in the repair of the damaged tissue thereby restoring the tissue back to normal, and this can help in reducing inflammation. Based on its benefits and unique characteristics in treating different pathologies, MSC is most frequently used in regenerative medicine and is now in the study of treating brain repair after ischemic stroke because of its potential for neuroregeneration (11, 10). A study by Zhang et al. explained how mesenchymal stem cells are transplanted into damaged tissues, examined the mechanisms used to prevent and treat damaged cells, and provided a summary of other clinical trials that are using MSC to treat ischemic stroke (11).

MSC releases paracrine factors that activate the modulation of microglia to differentiate into the glial cells and neurons to repair the damaged tissues. Studies showed that the paracrine action of MSC showed an improvement in neurotrophic effects and that paracrine signaling might be the main reason IS victims recover (11). Other mechanisms for MSC include cell migration, immunomodulation, neuroprotection, angiogenesis, and neural circuit reconstruction were also discussed by Zhang et al. (11). MSC is effective in treating cell migration by crossing the blood-brain barrier in migrating to the damaged cells. Mesenchymal stem cells migrate to the damaged brain of IS through the response of chemokines signals such as the MIP-1α and the

MCP-1; also, the increase of neurogenin-1 can increase the effectiveness of MSC, which in turn improves the effectiveness of the engraftment in the IS area (11). The immunomodulation and neuroprotective effects of MSC lower injuries that may occur hours or days after IS. MSC subdues the activation of the microglia cell and detain the death of neurons. It aids immunosuppression by the regulation of cytokine expression. MSC inhibits apoptosis by promoting endogenous repair in the neuroprotection of the damaged brain. It also increases the expression of the neurotrophic factors and this, in turn, is a major benefit in treating IS (11).

In angiogenesis, growth factors secreted by MSC such as IGF-1, BDNF, and bFGF increased angiogenesis in the ischemic core and the border zone. Angiogenesis also increases the flow of blood that is found in the brain tissue and this, in turn, benefits the endogenous neurogenesis and miRNA-210 promotes angiogenesis. In neural circuit reconstruction, MSC improves the neurological function after IS by the process of axonal plasticity and endogenous neurogenesis. When the axonal sprouting increases or enhances the connection between different cerebral areas, it repairs the connections between the neurons (11). In the study by Zhang et al. found that the middle cerebral artery occlusion (MCAO) model rats showed significant recovery when they tested with both allogeneic and heterogeneic MSC in the early preclinical trial. Twenty-one percent of the bone marrow-derived MSC (BMSC) were administered in the middle cerebral artery territory after intracarotid arterial injection. The treated rats showed functional improvement compared with the control rats (11). These same methods were then used with ischemic stroke rats using the intravenous injection of human MSC and showed similar results such as significant functional recovery results as shown with the treated (MCAO) models rats.

The MSC treatment increases the level of growth factors or receptors of BDNF and NGF in the ischemic tissue of the rats and a reduced level of apoptosis in the penumbral area. In clinical trials by Oy et al., autologous BMSC was introduced to 30 patients with ischemic stroke. They were divided into two groups (MSC and control). The MSC groups had 5 participants and received an intravenous infusion of 1 × 108 cells while the control group had 25 participants and did not receive MSC. BI and mRS were administered at regular intervals for up to 1 year after the onset of stroke. During their 12-month follow-up period, the Barthel index (p = 0.011, 0.017, and 0.115 at 3, 6, and 12 months, respectively) and modified Rankin Scale (mRS) score (p = 0.076, 0.171, and 0.286 at 3, 6, and 12 months, respectively) of the MSC group improved consistently compared to the control group (11, 14). This means that MSC transplantation is safe and showed an improvement in the patient's neurological condition.

A randomized controlled trial (RCT) by Assia et al. assessed the efficacy, feasibility, and safety of intravenous autologous bone marrow derived MSC in subacute ischemic stroke patients. Their study included 31 patients. Sixteen patients were treated with autologous MSC therapy, while 15 patients were placed in the control group. The MSC group showed significant improvements in motor National Institutes of Health stroke scale (NIHSS) (p = 0.004), motor Fugl-Meyer score (p = 0.028), and task-related fMRI activity in MI-4a (p = 0.031) in the primary motor cortex during the 2-year follow-up (11, 15). This shows that MSC treatment for subacute ischemic stroke was safe and feasible. Motor performance and task-related MI activity results suggest that MSC improved functional recovery via sensorimotor neuroplasticity (15).

Monoclonal antibody (mAb): an upcoming therapy in treating acute ischemic stroke (AIS) patients

Monoclonal antibodies (mAb) are used to treat cancer by interacting with specific targets of the cancer cells by bringing the T cells closer to cancer cells and this, in turn, kills the cancer cells (12). Since mAb has successfully been able to treat cancer patients, mAb might be a possible treatment for IS patients. The monoclonal antibody is a substitute antibody that restores, mimics, and enhances the immune system. It recognizes a particular protein form and is useful in producing large quantities of an antibody from a single B-cell clone and is highly specific (12). Monoclonal antibody therapy is an emerging treatment that may be able to help in treating the stroke outcomes of AIS patients outside of the 4.5-hour therapeutic window. Monoclonal antibodies can be given to a larger number of patients since they have a lifespan of days to weeks. Once the AIS occurs in the patient, anti-inflammatory and pro-inflammatory cytokines are then activated (13). This is where mAb will be given to help stop the receptors, and pathways that are caused by the inflammatory cytokines (13).

Monoclonal antibody therapy aids in neuronal repair and axonal growth by binding to receptors and surface markers; when this happens, it blocks the cells that inhibit neuronal cell growth (13). Blocking pro-inflammatory cytokine, and ion channels, and neurotransmitter receptors, enhancing anti-inflammatory cytokines and activating growth factors help mAb to increase the neuronal repair and regeneration to manage and treat the outcomes of AIS patients. Having a life span of more than an hour makes it beneficial and more effective in treatment options. Also, mAb was effective in reducing the infarct volume and neuronal performance in the animal model that had middle cerebral artery occlusion (13).

Monoclonal antibody therapy is administered against the toll-like receptor-4 (TLR4) and adhesion molecules (α-4 integrin) to stop the signaling molecules of the cascades to help reduce inflammation in MCAO mice. MCAO mice that were treated with a mAb against the TLR4 had a reduced volume of inaction and brain swelling compared to the MCAO mice that did not receive the treatment. Also, similar patterns were administered in human models using the natalizumab antibody which formed against leukocyte adhesion molecules, specifically against α-4 integrin. The natalizumab antibody was not successful as there was no significant reduction of infarct volume (13). Other studies showed that mAb was directed against an ICAM-1 in the embolic model of stroke followed by thrombolysis with tissue plasminogen activator (tPA) was conducted in rabbits, and results showed a decrease in the infiltration of inflammation which then leads to the decrease in neurological damage (13). Since mAb has been effective on experimental stroke models, it is certain to conduct further clinical research to assess the efficacy of human stroke patients (13).

Discussion

Statin therapy is important in secondary prevention therapy in treating stroke patients. In the study by Vitturi et al., participants that were given statin had a major benefit. The recurrence of stroke risk was reduced, and they also had better functional outcomes (9). According to this article and other previous studies, participants who were not given statin didn't have any better outcome; instead, they were at a higher risk of getting another stroke (9). Even though there is no optimal dosage of statin treatment for treating IS, results showed that administering a high dosage of simvastatin (40 mg) was effective in improving stroke prognosis. Participants who had the high-intensity statin did not show any major improvement and some reasons might be because of the expensive cost of those drugs which will allow the patient to stop or limit the amount of taking it because they cannot afford it (9). Both simvastatin 40 mg and high-intensity statins have proven to have a better benefit in IS patients and because of this, it might be administered to those patients that had a severe case. In short, statins are effective in preventing CVD in stroke patients. According to the authors Vitturi et al., since their studies were conducted in a hospital setting, and single-centered, instead of a community setting they encountered a higher risk of bias. They also involved all the consecutive cases and did not have any restrictions as to who to be admitted to the hospital.

The benefit of MSC in the treatment of other diseases has been an interest in seeing how it will benefit IS. MSC improves the damaged tissue of IS through various mechanisms. The authors did not discuss any limitations for their studies, but they talked about further research that needed to be done to study the pathways of angiogenesis and neurogenesis. The study supported that MSC transplantation is safe and effective in patients with cerebral recovery after ischemic stroke. Also, future studies should focus on large clinical trials, the safety and effective benefit for MSC, optimal dosages for MSC transplantation, and observe any adverse events in the order they can be used in clinical trials (11). On the other hand, mAb therapy has the potential to increase neuronal repair and regeneration in the brain of animal models. Therefore, there should be further research in assessing the efficacy of mAb on human stroke patients (13).

Conclusion

Ischemic stroke is a leading cause of neurological disability and requires fast treatment. Finding the right treatment that minimizes the long-term ischemic stroke will limit the number of cases per year. This review critically analyzes the safety and effectiveness of novel treatments for ischemic stroke. Statin therapy helps treat IS patients by improving functional performances, preventing recurrent stroke, and CVD events in patients. More studies are needed to verify the effect of statins in the stroke community. Also, MSC therapy is known to be safe and effective. Although it is still under research to test on a large number of patients, it might be a new treatment for the recovery of the neurological problems that are encountered in IS patients (11).

Having a specific mAb that targets the signaling pathways of stroke will unveil a better possible treatment in stroke therapy. However, even though mAb was effective in experimental stroke models, clinical research is needed to be done on human patients to see the benefit of this therapy (13). All of the treatments help improve the prognosis of IS, but further research is needed. Finding an effective mechanism for targeting the damaged cells of IS will be a greater benefit in treating it.

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Disclosures

The author has nothing to disclose.

References

1. Stroke [Internet]. Mayo Clinic. Mayo Foundation for Medical Education and Research; 2020 [cited 2020Dec18]. Available from: https://www.mayoclinic.org/diseases-conditions/stroke/symptoms-causes/syc-20350113
2. Ischemic Stroke [Internet]. Strokecenter.org. [cited 2020 Dec 18]. Available from: http://www.strokecenter.org/patients/about-stroke/ischemic-stroke/
3. Stroke Statistics [Internet]. Strokecenter.org. [cited 2020 Dec 18]. Available from: http://www.strokecenter.org/patients/about-stroke/stroke-statistics/
4. Stroke [Internet]. Nih.gov. [cited 2020 Dec 18]. Available from: https://www.nhlbi.nih.gov/health-topics/stroke
5. Ischemic Stroke [Internet]. Cedars-sinai.org. [cited 2020 Dec 18]. Available from: https://www.cedars-sinai.org/health-library/diseases-and-conditions/i/ischemic-stroke.html
6. Stroke: MedlinePlus medical encyclopedia. (n.d.). MedlinePlus - Health Information from the National Library of Medicine. https://medlineplus.gov/ency/article/000726.htm
7. Side effects of cholesterol-lowering statin drugs [Internet]. Webmd.com. [cited 2020 Dec 18]. Available from: https://www.webmd.com/cholesterol-management/side-effects-of-statin-drugs
8. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Statins: pros and cons. *Med Clin (Barc)*. 2018;150(10):398–402.
9. Vitturi BK, Gagliardi RJ. Effects of statin therapy on outcomes of ischemic stroke: a real-world experience in Brazil. *Arq Neuropsiquiatr*. 2020;78(8):461–7.

10. Saeedi P, Halabian R, Imani Fooladi AA. A revealing review of mesenchymal stem cells therapy, clinical perspectives, and Modification strategies. *Stem Cell Investig*. 2019;6:34.
11. Li J, Zhang Q, Wang W, Lin F, Wang S, Zhao J. Mesenchymal stem cell therapy for ischemic stroke: A look into treatment mechanism and therapeutic potential. *J Neurol* [Internet]. 2020; Available from: http://dx.doi.org/10.1007/s00415-020-10138-5
12. Monoclonal Antibodies [Internet]. Cancer.gov. 2019 [cited 2020 Dec 18]. Available from: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/monoclonal-antibodies
13. Woods D, Jiang Q, Chu X-P. Monoclonal antibody as an emerging therapy for acute ischemic stroke. *Int J Physiol Pathophysiol Pharmacol*. 2020;12(4):95–106.
14. Bang OY, Lee JS, Lee PH, Lee G (2005) Autologous mesenchymal stem cell transplantation in stroke patients. *Ann Neurol* 57(6):874–882. https://doi.org/10.1002/ana.20501)
15. Jaillard A, Hommel M, Moisan A, Zeffiro TA, Favre-Wiki IM, Barbieux-Guillot M, Vadot W, Marcel S, Lamalle L, Grand S, Detante O (2020) Autologous mesenchymal stem cells improve motor recovery in subacute ischemic stroke: a randomized clinical trial. *Trans Stroke Res*. https://doi.org/10.1007/s12975-020- 00787-z
16. Zhao W, Xiao ZJ, Zhao SP (2019, July 1) The benefits and risks of Statin therapy in ischemic stroke: A review of the literature. *Neurol India*. (2019, July 1). Neurology India: Free full text articles from Neurol India. https://neurologyindia.com/article.asp?issn=0028-3886;year=2019;volume=67;issue=4;spage=983;epage=992;aulast=Zhao#ref77