Remdesivir Reduces Time to Recovery in Adults Hospitalized With COVID-19: A Meaningful Step in Therapeutic Discovery

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med. 2020 May 22:NEJMoa2007764. doi: 10.1056/NEJMoa2007764. Online ahead of print.

Study Overview

Objective. To assess the clinical efficacy and safety of remdesivir in hospitalized adults with laboratory-confirmed COVID-19 and with evidence of lower respiratory tract involvement.

Design. Double-blinded, randomized, placebo-controlled, multicenter trial.

Setting and participants. Enrollment for the study took place between February 21, 2020, and April 19, 2020, at 60 trial sites and 13 subsites in the United States, Denmark, the United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore. Study participants included patients aged ≥ 18 years who were hospitalized and had laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as determined by a positive reverse transcription polymerase chain reaction assay on a respiratory specimen. Participants had evidence of lower respiratory tract infection at the time of enrollment; this was defined as radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO_2) ≤ 94% on room air, or requiring supplemental oxygen, mechan-

ical ventilation, or extracorporeal membrane oxygenation (ECMO). Exclusion criteria for study participation included abnormal liver enzymes (alanine aminotransferase, aspartate aminotransferase) more than 5 times the upper limit of normal range; impaired renal function or need for hemodialysis or hemofiltration; pregnancy or breastfeeding; or anticipated hospital discharge or transfer to another hospital within 72 hours of enrollment.

Intervention. Participants were randomized in a 1:1 ratio to the remdesivir group or the placebo group and were administered either intravenous infusions of remdesivir (200-mg loading dose on day 1, followed by a 100-mg maintenance dose daily on days 2 through 10, or until hospital discharge or death) or placebo for up to 10 days. Blinding was maintained by masking infusions with an opaque bag and tubing. Randomization was stratified by study site and disease severity at enrollment. Supportive care was delivered to all participants according to the standard of care at each trial site hospital. Clinical status, determined using an 8-category ordinal scale and the National Early Warning Score, was assessed daily for each participant while hospitalized (day 1 through day 29).

Blood samples for safety laboratory tests were collected, and oropharyngeal or nasopharyngeal swab testing was performed for viral RNA detection and quantification on days 1, 3, 5, 8, and 11. All serious adverse events (AEs) and grade 3/4 AEs that represented an increase in severity from day 1 and any grade 2 or higher suspected drug-related hypersensitivity reactions associated with the study drug or placebo administration were recorded.

Main outcome measures. The primary endpoint measure of this study was time to recovery, defined as the first day during the 28 days after enrollment on which a participant satisfied category 1 (ie, not hospitalized, no limitations of activities), 2 (ie, not hospitalized, limitation of activities, home oxygen requirement, or both), or 3 (ie, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care; hospitalization was extended for infection-control reason) on the 8-category ordinal scale. Secondary outcomes included all-cause mortality at 14 and 28 days after enrollment and grade 3/4 AEs and serious AEs that occurred during trial participation. Analysis of the primary outcome was performed using a log-rank test of the time to recovery comparing remdesivir with placebo group, stratified by disease severity.

The study's primary outcome was initially defined as a difference in clinical status as ascertained by the 8-category ordinal scale between groups of participants who were administered remdesivir versus placebo on day 15. Because of new knowledge gained external to the study about a more protracted COVID-19 clinical course than previously recognized, a change in primary outcome to time to recovery was proposed by trial statisticians, who were unaware of treatment assignments (72 participants had been enrolled) or outcome data (no interim data) on March 22, 2020, with subsequent amendment approval on April 2, 2020. On April 27, 2020, the Data and Safety Monitoring Board (DSMB) reviewed the interim study analysis (with data cutoff date of April 22, 2020) and recommended the report and mortality data to be provided to trial team members from the National Institute of Allergy and Infectious Diseases; these findings were subsequently made public.

Main results. A total of 1107 patients were assessed for eligibility, of whom 1063 underwent randomization, with 541 assigned to remdesivir and 522 to placebo. Results were unblinded early at the recommendation of DSMB due to findings from the interim analysis that showed reduced time to recovery in the group that received remdesivir. As of April 28, 2020, a total of 391 participants in the remdesivir group and 340 participants in the placebo group had completed the trial (day 29), recovered, or died. The mean age of participants was 58.9 ± 15.0 years, the majority were men (64.3%) and were White (53.2%), and the most common prespecified coexisting conditions were hypertension (49.6%), obesity (37.0%), and type 2 diabetes mellitus (29.7%). The vast majority of participants (88.7%) had severe COVID-19 disease at enrollment, defined as requiring invasive or noninvasive mechanical ventilation, requiring supplemental oxygen, $SpO_2 \leq 94\%$ on room air, or tachypnea (respiratory rate $\geq$ 24 breaths per minute).

Based on available data from 1059 participants (538 from the remdesivir group and 521 from the placebo group), those in the remdesivir group had a shorter median recovery time of 11 days (95% confidence interval [CI], 9-12) as compared to 15 days (95% CI, 13-19) in the placebo group, with a rate ratio for recovery of 1.32 (95% CI, 1.12-1.55; P < 0.001). Moreover, the odds of improvement on day 15 in the 8-category ordinal scale score were higher in the remdesivir group, compared to the placebo group (proportional odds model; odds ratio, 1.50; 95% CI, 1.18-1.91; P = 0.001; 844 participants).

Mortality rate by 14 days was numerically lower in the remdesivir group (7.1%) compared to the placebo group (11.9%), but the difference was not statistically significant (Kaplan-Meier, hazard ratio for death, 0.70; 95% CI, 0.47-1.04). Serious AEs were reported in 114 of the 541 (21.1%) participants in the remdesivir group and 141 of the 522 (27.0%) participants in the placebo group. Moreover, grade 3/4 AEs occurred in 156 (28.8%) participants in the remdesivir group and in 172 (33.0%) in the placebo group.

Conclusion. The study found that remdesivir, compared to placebo, significantly shortened time to recovery in adult patients hospitalized with COVID-19 who had evidence of lower respiratory tract infection.

Commentary

Since the initial reporting of a cluster of cases of pneumonia in Wuhan, China, on December 31, 2019, SARS-CoV-2 has been identified as the cause of this new disease (COVID-19), and to-date SARS-CoV-2 infection has affected more than 15.2 million people globally, with more than 3.9 million cases in the United States alone.[1] Despite an unprecedented global research effort, as well as public-private research partnerships, both in terms of scale and scope, an effective pharmacologic therapy for COVID-19 has so far eluded the scientific and medical community. Early trials of hydroxychloroquine and lopinavir-ritonavir did not demonstrate a clinical benefit in patients with COVID-19.[2,3] Moreover, the first randomized controlled trial of remdesivir in COVID-19, a nucleoside analogue prodrug and a broad-spectrum antiviral agent previously shown to have inhibitory effects on pathogenic coronaviruses, was an underpowered study, and thus inconclusive.[4] Thus, given the persistence of the COVID-19 pandemic and a current lack of effective vaccines or curative treatments, the study reported by Beigel and colleagues is timely and provides much needed knowledge in developing potential therapies for COVID-19.

The present report described the preliminary results of the first stage of the Adaptive Covid-19 Treatment Trial (ACCT-1), which aimed to evaluate the clinical efficacy and safety of intravenous remdesivir, as compared to placebo, in hospitalized adults with laboratory-confirmed COVID-19. The study itself was well-designed and conducted. The successful enrollment of more than 1000 participants randomized in a 1:1 ratio within a 2-month recruitment window, involving 60 international trial sites, shortly after the emergence of a new global pandemic was remarkable. This study provided the first evidence that remdesivir, an antiviral, can shorten time to recovery by approximately 31% compared to placebo in COVID-19 patients with lower respiratory tract involvement.

Interestingly, this beneficial effect of remdesivir on time to recovery was primarily observed in participants within the severe disease stratum (those requiring supplemental oxygen) at baseline (12 days in remdesivir group versus 18 days in placebo group), but not in those with mild-moderate disease at the time of study enrollment (5 days in either remdesivir or placebo group). Moreover,

the beneficial effects of remdesivir on reducing time to recovery was not observed in participants who required mechanical ventilation or ECMO at enrollment. Thus, these preliminary results suggest that COVID-19 disease severity and timing, particularly in patients who require supplemental oxygen but prior to disease progression towards requiring mechanical ventilation, may present a window of opportunity to initiate remdesivir treatment in order to improve outcomes. Further analysis utilizing data from the entire cohort, including outcomes data from the full 28-day follow-up period, may better delineate the subgroup of hospitalized COVID-19 patients who may benefit most from remdesivir. Last, safety data from the present study, along with that reported by Wang and colleagues,[4] provides evidence that intravenous remdesivir administration is likely safe in adults during the treatment period.

The preliminary results from the ACCT-1 provide early evidence that remdesivir shortens time to recovery in adult patients hospitalized for COVID-19 with pulmonary involvement. In light of these results, the US Food and Drug Administration issued an emergency use authorization for remdesivir on May 1, 2020, for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.[5] In addition, remdesivir has also recently been approved as a therapy for COVID-19 in Japan, Taiwan, India, Singapore, and the United Arab Emirates, and has received conditional approval for use by the European Commission.[6]

Although these are encouraging developments in the race to identify effective therapeutics for COVID-19, a number of unanswered questions regarding the administration of remdesivir in the treatment of this disease remain. For instance, in an open-label, randomized, multicenter trial of patients with severe COVID-19 not requiring mechanical ventilation, treatment with a 5-day course versus a 10-day course of intravenous remdesivir did not result in a significant difference in efficacy.[7] Thus, more studies are needed to better determine the shortest effective duration of remdesivir therapy in COVID-19 patients with different disease severity. Also, the mortality rate in COVID-19 patients who were treated with remdesivir remained high in the current study. Therefore, there is ample opportunity to evaluate treatment strat-

egies, including multidrug interventions with remdesivir, to reduce mortality and improve clinical outcomes in patients hospitalized with COVID-19.

Applications for Clinical Practice

Remdesivir shortens time to recovery in adult patients hospitalized with COVID-19 who require supplemental oxygen therapy. While much needs to be learned in order to optimize treatment of COVID-19, preliminary findings from the current study provide an important first step towards these discoveries.

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Oral Relugolix Yields Superior Testosterone Suppression and Decreased Cardiovascular Events Compared With GnRH Agonist

Shore ND, Saad F, Cookson MS, et. al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Eng J Med. 2020;382:2187-2196.

Study Overview

Objective. To evaluate the safety and efficacy of the highly selective oral gonadotropin-releasing hormone (GnRH) antagonist relugolix in men with advanced prostate cancer.

Design. Global, multicenter, randomized, open-label, phase 3 trial.

Intervention. Patients were randomized in a 2:1 ratio to receive either relugolix 120 mg once daily after receiving a single loading dose of 360 mg, or 22.5 mg of leuprolide acetate every 3 months. Patients in Japan and Taiwan received 11.25 mg of leuprolide. The randomization was stratified by age (> 75 years or ≤ 75 years), metastatic disease status, and geographic region (Asia, Europe, North and South America). The intervention period was 48 weeks.

Setting and participants. 1327 patients were screened, and 934 patients underwent randomization: 622 patients to the relugolix group and 308 to the leuprolide group. Patients had histologically or cytologically confirmed adenocarcinoma of the prostate. All patients had to have 1 of the following: evidence of biochemical or clinical relapse after primary curative therapy, newly diagnosed hormone-sensitive metastatic disease, or advance localized disease unlikely to be cured by local primary intervention. The patients with disease progression or rising prostate-specific antigen (PSA) had the option to receive enzalutamide or docetaxel after the confirmation of progression. Patients were excluded if they had a major cardiovascular event within 6 months of enrollment.

Main outcome measures. The primary endpoint was sustained castration rate, defined as the cumulative prob-

ability of testosterone suppression to ≤ 50 ng/dL while on study treatment from week 5 through week 48. Secondary endpoints included noninferiority of relugolix to leuprolide in regard to sustained castration rate. Superiority testing was performed if the noninferiority margin of –10 percentage points was met. Additional secondary endpoints were probability of testosterone suppression to ≤ 50 ng/dL on day 4 and day 15 and the percentage of patients with a > 50% decrease in PSA at day 15 and follicle-stimulating hormone (FSH) levels at the end of week 24.

Main results. The baseline characteristics were well balanced between the treatment groups. Approximately 30% of the patients in each group had metastatic disease. Approximately 50% of patients enrolled had biochemical recurrence following primary treatment for prostate cancer. The mean PSA was 104.2 ng/mL in the relugolix group and 68.6 ng/mL in the leuprolide group. The majority of patients had at least 1 cardiovascular risk factor (ie, tobacco use, obesity, diabetes, hypertension, or a history of a major adverse cardiac event [MACE]). Adherence to oral therapy was reported as 99% in both groups. The median follow-up time was 52 weeks; 90% of patients in the relugolix arm and 89% in the leuprolide arm completed 48 weeks of treatment.

Sustained testosterone suppression to ≤ 50 ng/dL from day 29 through week 48 was seen in 96.7% of patients in the relugolix group and 88.8% in the leuprolide group, which was determined to be noninferior. Additionally, relugolix was also found to be superior to leuprolide in regard to sustained testosterone suppression ($P < 0.001$). These results were consistent across all subgroups. Relugolix was also found to be superior to leuprolide for all secondary endpoints, including cumulative probability of castration on day 4 (56% vs 0%) and day 15 (98.7% vs 12%) and testosterone suppression to ≤ 20 ng/dL on day 15 (78.4% vs 1%). Confirmed PSA response on day 15 was seen in 79.4% of patients in the relugolix arm and in 19.8% in the leuprolide arm ($P < 0.001$). FSH suppression was greater in the relugolix arm compared with the leuprolide arm by the end of week 24. An increase of testosterone levels from baseline was noted in the leuprolide patients at day 4, with

the level decreasing to castrate level by day 29. In contrast, relugolix patients maintained castrate testosterone levels from day 4 throughout the intervention period. Testosterone recovery at 90 days was seen in 54% of patients in the relugolix group compared with 3% in the leuprolide group ($P = 0.002$).

The most frequent adverse event seen in both groups was hot flashes (54.3% in the relugolix group and 51.6% in the leuprolide group). The second most common adverse event report was fatigue, which occurred in 21.5% of patients in the relugolix arm and 18.5% in the leuprolide arm. Diarrhea was reported more frequently with relugolix than with leuprolide (12.2% vs 6.8%); however, diarrhea did not lead to discontinuation of therapy in any patient. Fatal events were reported more frequently in the leuprolide group (2.9%) compared with the relugolix group (1.1%). MACE were defined as nonfatal myocardial infarction, stroke, and death from any cause. After completing the intervention period of 48 weeks, the relugolix group had a 2.9% incidence of major cardiovascular events, compared with 6.2% in the leuprolide group. In patients having a medical history of cardiovascular events, the adverse event rate during the trial period was 3.6% in the relugolix group and 17.8% in leuprolide group. This translated into a 54% lower risk of MACE in the relugolix arm compared with the leuprolide arm.

Conclusion. The use of relugolix in advanced prostate cancer led to rapid, sustained suppression and faster recovery of testosterone level compared with leuprolide. Relugolix appeared safer to use for men with a medical history of cardiovascular events and showed a 54% lower risk of MACE than leuprolide.

Commentary

Relugolix is a highly selective oral GnRH antagonist that rapidly inhibits pituitary release of luteinizing hormone and FSH. The current phase 3 HERO trial highlights the efficacy of relugolix in regard to testosterone suppression, adding to potential therapeutic options for these men. Relugolix yielded superior sustained testosterone suppression to less than 50 ng/dL throughout the 48-week study period, meeting its primary endpoint. Additionally,

relugolix showed superiority in all secondary endpoints across all subgroups of patients. To date, the only GnRH antagonist on the market is degarelix, which is given as a monthly subcutaneous injection.[1] Injection-site reactions remain an issue with this formulation.

Cardiovascular disease is the leading cause of death in the United States, and it is known that men with prostate cancer have a higher incidence of cardiovascular disease.[2] While data regarding adverse cardiac outcomes with androgen deprivation therapy have been mixed, it is thought that this therapy increases the risk for MACE. There is mounting evidence that GnRH antagonists may have a less detrimental effect on cardiovascular outcomes compared with GnRH agonists. For example, a pooled analysis of 6 phase 3 trials showed a lower incidence of cardiovascular events in men with preexisting cardiovascular disease using the GnRH antagonist degarelix compared with GnRH agonists after 12 months of treatment.[3] Furthermore, a more recent phase 2 randomized trial showed that 20% of patients treated with a GnRH agonist developed cardiovascular events, compared to 3% in the GnRH antagonist group. The absolute risk reduction of cardiovascular events at 12 months was 18%.[4] The results of the current trial support such findings, showing a 54% reduction in MACE after 48 weeks of therapy when compared with leuprolide (2.9% in relugolix arm vs 6.2% in leuprolide arm). More importantly perhaps, in the subgroup of men with preexisting cardiovascular disease, the benefit was even greater, with a MACE incidence of 3.6% with relugolix compared with 17.8% with leuprolide.

Studies have also shown that second-generation antiandrogens such as enzalutamide are associated with an increased risk of death from cardiovascular causes. For example, data from the recently updated PROSPER trial, which evaluated the use of enzalutamide in men with nonmetastatic, castration-resistant prostate cancer, showed an increased risk of adverse events, including falls, fatigue, hypertension, and death from cardiovascular events.[5] Furthermore, adding second-generation antiandrogens to GnRH-agonist therapy is associated with a high risk of cardiovascular events in men with preexisting cardiovascular disease.[3]

These results were noted in all of the trials of second-generation antiandrogens, including enzalutamide, apalutamide, and darolutamide, in combination with GnRH agonists.[6-8] Taken together, one might consider whether the use of a GnRH antagonist would result in improved cardiovascular outcomes in high-risk patients.

In light of the efficacy of relugolix in regard to testosterone suppression highlighted in the current trial, it is likely that its efficacy in regard to cancer outcomes will be similar; however, to date there is no level 1 evidence to support this. Nevertheless, there is a clear association of adverse cardiovascular outcomes in men treated with GnRH agonists, and the notable 54% risk reduction seen in the current trial certainly would support considering the use of a GnRH antagonist for the subgroup of patients with preexisting cardiovascular disease or those at high risk for MACE. Further work is needed to define the role of GnRH antagonists in conjunction with second-generation antiandrogens to help mitigate cardiovascular toxicities.

Clinical Implications

The use of GnRH antagonists should be considered in men with advanced prostate cancer who have underlying cardiovascular disease to help mitigate the risk of MACE. Currently, degarelix is the only commercially available agent; however, pending regulatory approval, oral relugolix may be considered an appropriate oral option in such patients, with data supporting superior testosterone suppressive effects. Further follow-up will be needed.

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An Advance Care Planning Video Program in Nursing Homes Did Not Reduce Hospital Transfer and Burdensome Treatment in Long-Stay Residents

Study Overview

Objective. To examine the effect of an advance care planning video intervention in nursing homes on resident outcomes of hospital transfer, burdensome treatment, and hospice enrollment.

Design. Pragmatic cluster randomized controlled trial.

Setting and participants. The study was conducted in 360 nursing homes located in 32 states across the United States. The facilities were owned by 2 for-profit nursing home chains; facilities with more than 50 beds were eligible to be included in the study. Facilities deemed by corporate leaders to have serious organizational problems or that lacked the ability to transfer electronic health records were excluded. The facilities, stratified by the primary outcome hospitalizations per 1000 person-days, were then randomized to intervention and control in a 1:2 ratio. Leaders from facilities in the intervention group received letters describing their selection to participate in the advance care planning video program, and all facilities invited agreed to participate. Participants (residents in nursing homes) were enrolled from February 1, 2016, to May 31, 2018. Each participant was followed for 12 months after enrollment. All residents living in intervention facilities were offered the opportunity to watch intervention videos. The target population of the study was residents with advanced illness, including advanced dementia or advanced cardiopulmonary disease, as defined by the Minimum Data Set (MDS) variables, who were aged 65 and older, were long-stay residents (100 days or more), and were enrolled as Medicare fee-for-service beneficiaries. Secondary analysis included residents without advanced illness meeting other criteria.

Intervention. The intervention consisted of a selection of 5 short videos (6 to 10 minutes each), which had been previously developed and tested in smaller randomized trials. These videos cover the topics of general goals of care, goals of care for advanced dementia, hospice, hospitalization, and advance care planning for healthy patients, and use narration and images of typical treatments representing intensive medical care, basic medical care, and comfort care. The video for goals of care for advanced dementia targeted proxies of residents rather than residents themselves.

The implementation strategy for the video program included using a program manager to oversee the organization of the program's rollout (a manager for each for-profit nursing home chain) and 2 champions at each

facility (typically social workers were tasked with showing videos to patients and families). Champions received training from the study investigators and the manager and were asked to choose and offer selected videos to residents or proxies within 7 days of admission or readmission, every 6 months during a resident's stay, and when specific decisions occurred, such as transition to hospice care, and on special occasions, such as out-of-town family visits.

Video offering and use were captured through documentation by a facility champion using a report tool embedded in the facility's electronic health record. Champions met with the facility's program manager and study team to review reports of video use, identify residents who had not been shown a video, and problem-solve on how to reach these residents. Facilities in the control group used their usual procedures for advance care planning.

Main outcome measures. Study outcomes included hospitalization transfers per 1000 person-days alive among long-stay residents with advanced illness (primary outcome); proportion of residents with at least 1 hospital transfer; proportion of residents with at least 1 burdensome treatment; and hospice enrollment (secondary outcomes). Secondary outcomes also included hospitalization transfers for long-stay residents without advanced illness. Hospital transfers were identified using Medicare claims for admissions, emergency department visits, and observation stays. Burdensome treatments were identified from Medicare claims and MDS, including tube feeding, parenteral therapy, invasive mechanical intervention, and intensive care unit admission. Fidelity to video intervention was measured by the proportion of residents offered the videos and the proportion of residents shown the videos at least once during the study period.

Main results. A total of 360 facilities were included in the study, 119 intervention and 241 control facilities. For the primary outcome, 4171 residents with advanced illness were included in the intervention group and 8308 residents with advanced illness were included in the control group. The average age was 83.6 years in both groups. In the intervention and control groups, respectively, 71.2% and 70.5% were female, 78.4% and 81.5% were White, 68.6% and 70.1% had advanced dementia at baseline, and 35.4% and 33.4% had advanced congestive heart failure or chronic obstructive pulmonary disease at baseline. Approximately 34% of residents received hospice care at baseline. In the intervention and control groups, 43.9% and 45.3% of residents died during follow-up, and the average length of follow-up in each group was 253.1 days and 252.6 days, respectively.

For the primary outcome of hospital transfers per 1000 person-days alive, there were 3.7 episodes (standard error 0.2) in the intervention group and 3.9 episodes in the control group (standard error 0.3); the difference was not statistically significant. For residents without advanced illness, there also was no difference in the hospital transfer rate. For other secondary outcomes, the proportion of residents in the intervention and control groups with 1 or more hospital transfer was 40.9% and 41.6%, respectively; the proportion with 1 or more burdensome treatment was 9.6% and 10.7%; and hospice enrollment was 24.9% and 25.5%. None of these differences was statistically significant. In the intervention group, 55.6% of residents or proxies were offered the video intervention and 21.9% were shown the videos at least once. There was substantial variability in the proportion of residents in the intervention group who were shown videos.

Conclusion. The advance planning video program did not lead to a reduction in hospital transfer, burdensome treatment, or changes in hospice enrollment. Acceptance of the intervention by residents was variable, and this may have contributed to the null finding.

Commentary

Nursing home residents often have advanced illness and limited functional ability. Hospital transfers may be burdensome and of limited clinical benefit for these patients, particularly for those with advanced illness and limited life expectancy, and are associated with markers of poor quality of end-of-life care, such as increased rates of stage IV decubitus ulcer and feeding-tube use towards the end of life.[1] Advance care planning is associated with less aggressive care towards the end of life for persons with

advanced illness,[2] which ultimately improves the quality of end-of-life care for these individuals. Prior interventions to improve advance care planning have had variable effects, while video-based interventions to improve advance care planning have shown promise.[3]

This pragmatic randomized trial assessed the effect of an advance care planning video program on important clinical outcomes for nursing home residents, particularly those with advanced illness. The results, however, are disappointing, as the video intervention failed to improve hospital transfer rate and burdensome treatment in this population. The negative results could be attributed to the limited adoption of the video intervention in the study, as only 21.9% of residents in the intervention group were actually exposed to the intervention. What is not reported, and is difficult to assess, is whether the video intervention led to advance care planning, as would be demonstrated by advance directive documentation and acceptance of goals of care of comfort. A per-protocol analysis may be considered to demonstrate if there is an effect on residents who were exposed to the intervention. Nonetheless, the low adoption rate of the intervention may prompt further investigation of factors limiting adoption and perhaps lead to a redesigned trial aimed at enhancing adoption, with consideration of use of implementation trial designs.

As pointed out by the study investigators, other changes to nursing home practices, specifically on hospital transfer, likely occurred during the study period. A number of national initiatives to reduce unnecessary hospital transfer from nursing homes have been introduced, and a reduction in hospital transfers occurred between 2011 and 2017[4]; these initiatives could have impacted staff priorities and adoption of the study intervention relative to other co-occurring initiatives.

Applications for Clinical Practice

The authors of this study reported negative trial results, but their findings highlight important issues in conducting trials in the nursing home setting. Additional demonstration of actual effect on advance care planning discussions and documentation will further enhance our understanding of whether the intervention, as tested, yields changes in practice on advance care planning in nursing homes. The pragmatic clinical trial design used in this study accounts for real-world settings, but may have limited the study's ability to account for and adjust for differences in staff, settings, and other conditions and factors that may impact adoption of and fidelity to the intervention. Quality improvement approaches, such as INTERACT, have targeted unnecessary hospital transfers and may yield positive results.[5] Quality improvement approaches like INTERACT allow for a high degree of adaptation to local procedures and settings, which in clinical trials is difficult to do. However, in a real-world setting, such approaches may be necessary to improve care.

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Dapagliflozin Improves Cardiovascular Outcomes in Patients With Heart Failure and Reduced Ejection Fraction

McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995-2008.

Study Overview

Objective. To evaluate the effects of dapagliflozin in patients with heart failure with reduced ejection fraction in the presence or absence of type 2 diabetes.

Design. Multicenter, international, double-blind, prospective, randomized, controlled trial.

Setting and participants. Adult patients with symptomatic heart failure with an ejection fraction of 40% or less and elevated heart failure biomarkers who were already on appropriate guideline-directed therapies were eligible for the study.

Intervention. A total of 4744 patients were randomly assigned to receive dapagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. Randomization was stratified by the presence or absence of type 2 diabetes.

Main outcome measures. The primary outcome was the composite of a first episode of worsening heart failure (hospitalization or urgent intravenous therapy) or cardiovascular death.

Main results. Median follow-up was 18.2 months; during this time, the primary outcome occurred in 16.3% (386 of 2373) of patients in the dapagliflozin group and in 21.2% (502 of 2371) of patients in the placebo group (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.65-0.85; $P < 0.001$). In the dapagliflozin group, 237 patients (10.0%) experienced a first worsening heart failure event, as compared with 326 patients (13.7%) in the placebo group (HR, 0.70; 95% CI, 0.59-0.83). The dapagliflozin group had lower rates of death from cardiovascular causes (9.6% vs 11.5%; HR, 0.82; 95% CI, 0.69-0.98) and from any causes (11.6% vs 13.9%; HR, 0.83; 95% CI, 0.71-0.97), compared to the placebo group. Findings in patients with diabetes were similar to those in patients without diabetes.

Conclusion. Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes.

Commentary

Inhibitors of sodium-glucose cotransporter 2 (SGLT-2) are a novel class of diabetic medication that decrease renal glucose reabsorption, thereby increasing urinary glucose excretion. In several large clinical trials of these medications for patients with diabetes, which were designed to meet the regulatory requirements for cardiovascular safety in novel diabetic agents, investigators unexpectedly found that SGLT-2 inhibitors were associated with a reduction in cardiovascular events, driven by a reduction in heart failure hospitalizations. The results of EMPA-REG OUTCOME, the first of these trials, showed significantly lower risks of both death from any cause and hospitalization for heart failure in patients treated with empagliflozin.[1] This improvement in cardiovascular outcomes was subsequently confirmed as a class effect of SGLT-2 inhibitors in the CANVAS Program (canagliflozin) and DECLARE TIMI 58 (dapagliflozin) trials.[2,3]

While these trials were designed for patients with type 2 diabetes who had either established cardiovascular disease or multiple risk factors for it, most patients did not have heart failure at baseline. Accordingly, despite a signal toward benefit of SGLT-2 inhibitors in patients

with heart failure, the trials were not powered to test the hypothesis that SGLT-2 inhibitors benefit patients with heart failure, regardless of diabetes status. Therefore, McMurray et al designed the DAPA-HF trial to investigate whether SGLT-2 inhibitors can improve cardiovascular outcomes in patients with heart failure with reduced ejection fraction, with or without diabetes. The trial included 4744 patients with heart failure with reduced ejection fraction, who were randomly assigned to dapagliflozin 10 mg once daily or placebo, atop guideline-directed heart failure therapy, with randomization stratified by presence or absence of type 2 diabetes. Investigators found that the composite primary outcome, a first episode of worsening heart failure or cardiovascular death, occurred less frequently in patients in the dapagliflozin group compared to the placebo group (16.3% vs 21.2%; HR, 0.74; 95% CI, 0.65-0.85; *P* < 0.001). Individual components of the primary outcome and death from any cause were all significantly lower, and heart failure–related quality of life was significantly improved in the dapagliflozin group compared to placebo.

DAPA-HF was the first randomized study to investigate the effect of SGLT-2 inhibitors on patients with heart failure regardless of the presence of diabetes. In addition to the reduction in the above-mentioned primary and secondary endpoints, the study yielded other important findings worth noting. First, the consistent benefit of dapagliflozin on cardiovascular outcomes in patients with and without diabetes suggests that the cardioprotective effect of dapagliflozin is independent of its glucose-lowering effect. Prior studies have proposed alternative mechanisms, such as diuretic function and related hemodynamic actions, effects on myocardial metabolism, ion transporters, fibrosis, adipokines, vascular function, and the preservation of renal function. Future studies are needed to fully understand the likely pleiotropic effects of this class of medication on patients with heart failure. Second, there was no difference in the safety endpoints between the groups, including renal adverse events and major hypoglycemia, implying dapagliflozin is as safe as placebo.

There are a few limitations of this trial. First, as the authors point out, the study included mostly white males— less than 5% of participants were African Americans—

and the finding may not be generalizable to all patient populations. Second, although all patients were already treated with guideline-directed heart failure therapy, only 10% of patients were on sacubitril–valsartan, which is more effective than renin–angiotensin system blockade alone at reducing the incidence of hospitalization for heart failure and death from cardiovascular causes. Also, mineralocorticoid receptor blockers were used in only 70% of the population. Finally, since the doses were not provided, whether patients were on the maximal tolerated dose of heart failure therapy prior to enrollment is unclear.

Based on the results of the DAPA-HF trial, the Food and Drug Administration approved dapagliflozin for the treatment of heart failure with reduced ejection fraction on May 5, 2020. This is the first diabetic drug approved for the treatment of heart failure.

Applications for Clinical Practice

SGLT-2 inhibitors represent a fourth class of medication that patients with heart failure with reduced ejection fraction should be initiated on, in addition to beta blocker, ACE inhibitor/angiotensin receptor blocker/neprilysin inhibitor, and mineralocorticoid receptor blocker. SGLT-2 inhibitors may be especially applicable in patients with heart failure with reduced ejection fraction and relative hypotension, as these agents are not associated with a significant blood-pressure-lowering effect, which can often limit our ability to initiate or uptitrate the other main 3 classes of guideline-directed medical therapy.

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