Is Sitagliptin Plus Glargine Noninferior to Basal–Bolus Insulin for Inpatient Management of Type 2 Diabetes?


Study Overview

Objective. To compare the safety and efficacy of basal–bolus insulin therapy with sitagliptin plus insulin glargine in type 2 diabetes patients admitted to general medicine and surgical wards.

Design. Multicenter, prospective, open-label, noninferiority randomized clinical trial.

Setting and participants. Type 2 diabetes patients aged 18 to 80 years admitted to the general medicine and surgery services at one of 5 academic-based US hospitals were recruited. Eligible participants presented with a random blood glucose concentration between 140 and 400 mg/dL and were treated at home with diet, oral agents, or oral agents plus insulin at a maximum daily dose of 0.6 units/kg. Among those excluded were patients recently treated with a dipeptidyl peptidase-4 (DPP-4) inhibitor or glucagon-like peptide-1 (GLP-1) agonist, patients with clinically relevant hepatic disease, patients who were not eating for more than 48 hours, and those with an estimated glomerular filtration rate (eGFR) < 30 mL/min.

Intervention. Participants were randomly assigned to receive basal–bolus insulin therapy (BBI) with glargine once daily plus rapid-acting insulin before meals or sitagliptin plus glargine (SPG) once daily. Those in the SPG group received sitagliptin 100 mg/day if their eGFR was > 50 mL/min and sitagliptin 50 mg/day if their eGFR was 30 to 50 mL/min. If the eGFR fell below 30 mL/min during the hospitalization, sitagliptin was reduced to 25 mg/day. Glargine doses for those in the SPG group were started at 0.2 units/kg if randomization blood glucose was 140–200 mg/dL and 0.25 units/kg if randomization glucose was 201–400 mg/dL. Patients aged 70 or older or with an eGFR < 50 mL/min started with a daily glargine dose of 0.15 units/kg. For the BBI group, a total daily insulin dose of 0.4 units/kg was initiated for those with blood glucose levels between 140 and 200 mg/dL, and 0.5 units/kg for those with randomization glucose between 201 and 400 mg/dL. Half of this daily dose was given as glargine and the other half was distributed evenly across 3 pre-meal doses. Both the BBI and SPG groups received pre-meal and bedtime correction doses of rapid-acting insulin for glucose levels above 140 mg/dL. Blood glucose concentrations were
measured fasting, before meals, and at bedtime or every 6 hours for patients who were not eating. Target fasting and pre-meal blood glucose levels were 100 to 140 mg/dL. Investigators and participants were not blinded to group assignment and glucose control was managed by the primary medical or surgical team.

Main outcomes measure. The primary outcome for this trial was noninferiority for differences between the SPG and BBI groups in glycemic control. Secondary endpoints included differences in the number of hypoglycemic and hyperglycemic events, the number of blood glucose values between 70 and 140 mg/dL and between 70 and 180 mg/dL, and the number of treatment failures (defined as 2 consecutive blood glucose values > 240 mg/dL or mean daily glucose > 240 mg/dL), length of hospital stay, total daily dose of insulin, number of insulin injections per day, transfer to the intensive care unit, and hospital complications and mortality.

Main results. A total of 138 patients in the SPG group and 139 patients in the BBI group completed the study and were included in this analysis. Of these 277 patients, 84% were admitted to a medicine ward and 16% were admitted to a surgical ward. The average age of participants was approximately 57 years, the average BMI was approximately 35 kg/m², and the average duration of diabetes was approximately 10 years. These baseline characteristics as well as ethnic origin, sex, and baseline A1c (approximately 40% of patients in both groups had a baseline A1c between 7% and 9%) did not differ between groups. Prior to admission, approximately 40% of patients in both groups were managed with oral drugs alone, approximately 25% were managed with insulin alone, and about 22% were managed with insulin and oral therapy.

With respect to the primary outcome, both groups had similar mean daily blood glucose concentrations (171 mg/dL in SPG and 169 mg/dL in BBI) throughout the hospitalization, meeting the noninferiority threshold for glycemic control between groups. As for secondary outcomes, the mean proportion of blood glucose readings between 70 and 140 mg/dL, 70 and 180 mg/dL, and 100 and 140 mg/dL did not differ between groups. Pre-meal and bedtime blood glucose concentrations were also similar in both groups. There was a significant difference between groups in average daily insulin dose (24 units in SPG versus 34 units in BBI), total units of insulin per kg per day (0.2 units/kg in SPG versus 0.3 units/kg in BBI), and number of insulin injections per day (2.2 in SPG versus 2.9 in BBI). There was no difference in the number of hypoglycemic or hyperglycemic events, length of hospital stay (approximately 4 days in both groups), and rates of complications (including acute respiratory failure, acute kidney injury, and myocardial infarction) between groups.

Conclusion. Inpatient treatment with sitagliptin plus glargine was noninferior to basal–bolus insulin therapy in measurements of glycemic control.

Commentary
Approximately 25% to 30% of adult patients admitted to general medical and surgical wards and critical care units have type 2 diabetes [1]. Maintaining adequate blood sugar control is important, as both hyperglycemia and hypoglycemia have been associated with adverse outcomes. Although group consensus statements differ slightly with respect to recommended target glucose levels, generally the recommended range in a noncritical inpatient setting is 140 to 180 mg/dL [2,3]. Establishing and maintaining these levels can often be very challenging. Barriers to achieving adequate glucose control in the inpatient setting include changes in a patients’ nutrition status, renal function, pain level, the use of glucocorticoids, and the development of infections. In addition, a significant gap in knowledge can exist from provider to provider in terms of how to appropriately initiate and titrate insulin regimens. To circumvent this, many hospitals have created built-in order sets and protocols in the electronic medical record for basal–bolus correction insulin regimens. While these protocols may have improved many parameters of inpatient diabetes management at several institutions, improper initiation and execution of these protocols still occur. Also, at times the priorities of the medical team can shift so that titration of the insulin regimen may not occur frequently enough. Overall, simplification of inpatient glucose management would certainly be a welcomed change.

Unfortunately, there is a dearth of studies that investigate the role of oral therapy in the inpatient setting. In general, oral medications are discontinued upon admission and insulin is the recommended standard of care. In this study, Pasquel and colleagues investigated the use of the DPP-4 inhibitor sitagliptin in the inpatient setting. Unlike some of the other classes of oral agents used in the outpatient setting, DPP-4 inhibitors are generally
well tolerated. A major advantage of DPP-4 inhibitors is that, with dose titration, they can also be used in mild to moderate renal failure. However, because DPP-4 inhibitors work in the prandial setting, they are not effective in the NPO patient. In this study, both the SPG group and BBI group had similar average daily blood glucose levels after the first day of therapy and throughout the hospitalization (171 mg/dL in SPG versus 169 mg/dL in BBI). Since the key finding here was noninferiority for blood sugar control between the treatments, the major differences between SPG and BBI therapy should be highlighted.

One benefit of SPG versus BBI therapy is that replacement of bolus insulin injections with a once-daily pill reduces the need for frequent bolus insulin dose titration. Nonetheless, renal function should be monitored frequently, as sitagliptin dose adjustments may be required, and the importance of bedside glucose checks should not be diminished, as some patients may not maintain adequate control on this regimen and will need to be transitioned to BBI therapy. Both treatment groups received correctional insulin doses in the prandial setting if their pre-meal glucose levels met a specific threshold. Overall, the SPG group required significantly fewer total insulin injections per day (2.2 injections in SPG versus 2.9 injections in BBI, \( P < 0.001 \)). Though this difference is rather small, the need to administer fewer insulin injections would certainly be beneficial to nursing staff, who often care for several type 2 diabetes patients at once. It would have been interesting to know how many patients in each group were free of any correctional insulin doses or how many were adequately controlled with just 1 prandial injection per day. Although it cannot be concluded from this study, it could be expected that the reduced need for bolus insulin dose titration and fewer total insulin injections associated with oral therapy would result in less insulin dosing error and perhaps greater patient satisfaction.

It is important to keep in mind that initiating a DPP-4 inhibitor with basal insulin may not be an appropriate option for all admitted type 2 diabetes patients. It can be a beneficial alternative to insulin for the select group of patients included in this study: those treated at home with diet alone, oral therapy alone, or oral therapy plus insulin.

While the potential for implementation of SPG therapy in an inpatient setting does exist, there are some limitations to this study that make further investigation necessary. Though the patent on Januvia (sitagliptin’s trade name) expires in 2017, sitagliptin is currently a very expensive drug. Therefore, a cost-benefit analysis of SPG therapy versus insulin therapy alone should be undertaken. Also, this was an unblinded study, which may have resulted in more attentive, prioritized blood sugar management than what would typically occur in an inpatient setting. Also, the providers’ level of expertise on insulin management in this study may not be generalized to all inpatient medical and surgical providers. Despite these limitations, this study may have a profound impact on inpatient diabetes management, since a less labor-intensive alternative to basal–bolus insulin therapy may present a more attractive option for many inpatient providers.

**Applications for Clinical Practice**

This study could pave the way for a practice-changing method of inpatient glucose management for a select group of patients who do not have severely uncontrolled type 2 diabetes. One should keep in mind that cost could be a barrier to implementation of sitagliptin in hospitals, and that while the bolus dose of insulin can be replaced with sitagliptin, patients may still need correctional doses of insulin to maintain target ranges. Also, a daily assessment of glucose control is still necessary in order to determine if a change in management is needed. Therefore, the sitagliptin plus glargine option should not be viewed as a “shortcut” therapy, but rather as a potentially less labor-intensive option that may increase the ability to prioritize blood sugar management in the inpatient setting.

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**References**

Treatment of Biochemical Recurrence After Prostatectomy: A Step Forward


Study Overview

Objective. To evaluate the impact on overall survival of adding antiandrogen (bicalutamide) therapy to radiation in patients with prostate cancer who have an elevated prostate-specific antigen (PSA) after radical prostatectomy (either as persistence or as a relapse) and no evidence of metastatic disease.

Design. Phase III, randomized, double-blind, placebo-controlled trial.

Setting and participants. The trial was designed by NRG Oncology (Philadelphia, PA), sponsored by the National Cancer Institute, and conducted at NRG Oncology member sites, which included community-based hospitals. Eligible patients had undergone radical prostatectomy and had disease that was originally assessed, on the basis of pathological testing, as tumor stage T2 (confined to the prostate but with a positive surgical margin) or T3 (with histologic extension of tumor beyond the prostate capsule) without nodal involvement. Patients also had to have a detectable PSA level between 0.2 and 4.0 ng/mL at least 8 weeks after surgery. All the patients underwent abdominal and pelvic computed tomography (CT) and bone scans to rule out metastatic disease. Patients who received prior chemotherapy or radiation therapy for prostate cancer were excluded. Most patients had not received prior hormonal therapy for prostate cancer.

Intervention. All eligible patients received salvage radiation therapy within 12 weeks after randomization. Radiation was directed to the original prostatic site, the tumor resection bed, and the membranous urethra at a total dose of 64.8 Gy given in 36 daily fractions. In addition to the radiation therapy, patients were randomly assigned to receive either 150 mg of bicalutamide or 1 placebo tablet daily, beginning at the initiation of radiation therapy and continuing for 24 months. Tablets were administered in a double blind fashion. Follow-up evaluations occurred every 3 months for 2 years, then every 6 months for 3 years, and then yearly. Bone and CT scans were performed either at biochemical recurrence or as indicated clinically. If metastatic disease was detected on follow up or if the serum PSA level rose to more than 4.0 ng/mL, maximum androgen blockade was recommended.

Main outcome measure. The main outcome was overall survival rate at 12 years. Secondary end points were disease-specific death, distant metastases, local disease progression, non–disease-specific death, any prostate cancer progression including a second biochemical recurrence, and adverse events.

Main results. 840 patients were randomized between March 1998 and March 2003, with 760 patients eligible for evaluation (384 patients in bicalutamide group and 376 in placebo group). Demographic and tumor-related characteristics of the 2 groups were similar. In both groups the majority of patients were white (89.6% in bicalutamide arm; 86.2 in placebo), had Karnofsky performance status score of 100% (77.1 % in bicalutamide arm; 74.5% in placebo), and had positive surgical margin (75% in bicalutamide arm; 74.7% in placebo). Median age was 65 years, and median PSA level at trial entry was 0.6 ng/mL. The median follow-up among the surviving patients was 13 years.

A total of 21 patients in the bicalutamide group and 46 patients in the placebo group died from prostate cancer. The actuarial rate of overall survival at 12 years was 76.3% in the bicalutamide group and 71.3% in the placebo group (hazard ratio [HR] for death 0.77 [95% confidence interval [CI] 0.59 to 0.99; P = 0.04), resulting in a 23% relative reduction in the risk of death in patients who received bicalutamide. The 12-year incidence of death from prostate cancer was 5.8% in the bicalutamide group versus 13.4% in the placebo group (HR 0.49 [95% CI 0.32 to 0.74]; P < 0.001), resulting in a 51% lower rate of death from prostate cancer in bical-
utamide patients. Post hoc subgroup analyses showed that the greatest overall survival benefit was seen in subgroups of patients with more aggressive prostate cancer, such as those with high PSA level at trial entry (1.5 to 4.0 ng/mL) or Gleason score of 7. There were too few patients with Gleason scores of 8, 9, or 10 to draw meaningful conclusions about this subgroup. There appeared to be a larger benefit in patients with positive surgical margins than in those with negative surgical margins.

Adherence to radiation therapy was similar between the 2 trial groups, and addition of bicalutamide to radiation therapy did not result in an increase in adverse events associated with radiation therapy, such as cystitis, colitis, or sexual dysfunction. The rates of hot flashes and cardiovascular deaths were not significantly higher in the bicalutamide group than in the placebo group. However, gynecomastia was reported significantly more frequently in the bicalutamide group (69.7%) than in the placebo group (10.9%, P < 0.001).

Conclusion. The addition of 24 months of antiandrogen therapy with daily bicalutamide to salvage radiation therapy resulted in significantly higher rates of long-term overall survival and lower incidence of death from prostate cancer as compared to the addition of placebo. This benefit appeared to be without a significant cost in terms of toxicity.

Commentary

Prostate cancer is the second most common cancer in men worldwide, with an estimated 1,618,000 cases and 366,000 deaths in 2015 [1]. The current lifetime risk of developing prostate cancer for men living in the United States is estimated to be 1 in 6 [2]. Most prostate cancers are diagnosed in the localized stage, which is often treated with radical prostatectomy. All prostate tissue is removed during a successful radical prostatectomy. Postoperatively, detectable serum PSA is indicative of residual prostatic tissue, which presumably represents disease recurrence. This elevation in PSA after surgery in the absence of systemic metastatic disease is termed biochemical recurrence. The current standard of care for patients who develop biochemical recurrence is salvage radiation therapy. The prognosis for these patients is related to initial tumor characteristics—grade, volume and local stage. However, approximately 50% of the patients who are treated with salvage radiation therapy for biochemical recurrence will have further disease progression and may ultimately die from prostate cancer [3,4]. This is especially true when aggressive disease features are present. Radiation therapy combined with androgen-deprivation therapy using GnRH agonists or antiandrogen therapy (bicalutamide, flutamide) prolongs survival among some men with an intact prostate. This combination represents a rationale approach to prolong survival among men who develop non-metastatic biochemical relapse after radical prostatectomy.

The study by Shipley and colleagues reports the long-term outcomes of a randomized trial comparing salvage radiation plus 2 years of antiandrogen therapy to salvage radiation and placebo. Starting daily bicalutamide 150 mg orally with salvage radiation and continuing for 2 years was associated with a 23% improvement in overall survival and a 51% lower rate of death from prostate cancer, as compared to the placebo group. The number needed to treat (NNT) with bicalutamide to prevent one death from prostate cancer over 12 years was 20. By comparison, standard treatment of prostate cancer with surgery or radiation has an NNT of 27, which demonstrates the magnitude of the benefit of addition of antiandrogen therapy to salvage radiation. The benefit appears to be greatest in patients with poor prognostic factors such as higher Gleason scores (8 to 10), a higher PSA level at entry (0.7 to 4.0 ng/mL), or positive surgical margins. In contrast, patients with lower Gleason score or negative margins seemed to benefit less from the addition of antiandrogen therapy to salvage radiation. Two years of bicalutamide was not associated with increased incidence of radiation-related toxicities or cardiovascular death. As expected, the primary adverse effect of bicalutamide was gynecomastia, which was seen in 70% of the men treated. This adverse effect can be distressing but can be mitigated by prophylactic radiation of the breast or by the administration of tamoxifen, which were not done as preventative measures in this trial.

While the addition of bicalutamide to radiation did show a clear benefit to overall survival, questions remain about whether bicalutamide is the best drug to use. As the authors note, at present GnRH agonists such as leuprolide are considered first-line hormonal therapy with radiation for most patients with prostate cancer, and bicalutamide at the dose used in this study (150 mg) is not approved. We do not know how GnRH agonists will perform either as a single agent or in combination with antiandrogen for patients who develop biochemical...
relapse, as the use of GnRH agonists with radiation therapy has not been evaluated in patients who develop biochemical relapse in randomized clinical trials. Two trials exploring the use of androgen deprivation therapy with salvage radiation therapy in patients with biochemical recurrence (Radiotherapy and Androgen Deprivation in Combination After Local Surgery–Hormone Duration [RADICALS-HD] and the Groupe d’Etude des Tumeurs Uro-Génitales [GETUG]-16 trial) have finished enrollment; however, we will have to wait until the overall survival data matures before drawing any meaningful conclusions from them [5,6]. We know that patients with certain aggressive disease features based on tumor stage, grade, and volume are more likely to develop biochemical recurrence. As such, it is logical to consider evaluating the role of androgen deprivation therapy with adjuvant radiation therapy in patients who are at high risk of biochemical relapse with the goal of prolonging survival and reducing the risk of metastases. The RADICALS (Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer) trial, which is evaluating the role of androgen deprivation therapy after adjuvant radiation therapy in patients who are at high risk of developing biochemical relapse, will help to address this issue.

Applications for Clinical Practice

Adding an antiandrogen agent (bicalutamide) to salvage radiation therapy in this randomized, double-blind, placebo-controlled trial resulted in higher rates of overall survival, disease-specific survival, and metastasis-free interval than radiation therapy alone for patients who developed biochemical relapse after radical prostatectomy for pathological T2/T3 and node-negative prostate cancer. We eagerly await the results of clinical trials evaluating the role of GnRH agonists in combination with salvage radiation therapy in patients in this setting. Given the long natural history of prostate cancer and the relatively low event rate, such studies can take over a decade to show differences in overall survival. Thus, until such data is available, 24 months of bicalutamide in combination with salvage radiation should be considered the new standard of care for patients (especially those at high risk) who develop non-metastatic biochemical relapse after prostatectomy.

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References