tumor. The efficacy of RAI is dependent on many factors including sites of disease, patient preparation, tumor characteristics, and dose of radiation administered.

EBRT is currently used much less frequently than RAI in the management of differentiated thyroid cancer. Its main use has been for palliative treatment of locally advanced, unresectable, or metastatic disease in primarily noniodine-avid tumors. It has also been suggested for use in older patients (age 55 years or older) with gross extrathyroidal extension at the time of surgery (T4 disease), or in younger patients with T4b or extensive T4a disease and poor histologic features, with tumors that are strongly suspected to not concentrate iodine. The use of EBRT in other settings is not well established [3,4].

Treatment benefits of RAI in DTC have been extensively studied; however, this is the largest study that has examined long-term survival in a cohort of just under 12,000 patients with stage IV DTC. The results from this large cohort with advanced disease further demonstrates improved overall survival in stage IV DTC patients treated with RAI at 5 and 10 years. It is clear that RAI is the first-line adjuvant radiation therapy of DTC and should remain the standard of care in thyroid cancer management.

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Inhaled Corticosteroid Plus Long-Acting Beta-Agonist for Asthma: Real-Life Evidence

Woodcock A, Vestbo J, Bakerly ND, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet 2017.

Study Overview

Objective. To determine the effectiveness of asthma treatment using fluticasone furoate plus vilanterol in a setting that is closer to usual clinical practice.

Design. Open-label, parallel group, randomised controlled trial.

Setting and participants. The study was conducted at 74 general practice clinics in Salford and South Manchester, UK, between Nov 2012 and Dec 2016. Patients with a general practitioner's diagnosis of symptomatic asthma and on maintenance inhaler therapy (either inhaled corticosteroid [ICS] alone or in combination with a long-acting bronchodilator [LABA]) were recruited. Patients with recent history of life-threatening asthma, COPD, or concomitant life-threatening disease were excluded. Participants were randomly assigned through a centralized randomization service and stratified by Asthma Control Test (ACT) score and by previous asthma maintenance therapy (ICS or ICS/LABA). Only those with an ACT score < 20 were included in the study.

Intervention. Patients were randomized to receive either a combination of fluticasone furoate and vilanterol (FF/VI) delivered by novel dry powder inhalation (DPI) (Ellipta) or to continue with their maintenance therapy. General practitioners provided care in their usual manner and could continuously optimize therapy according to their clinical opinion. Treatments were dispensed by community pharmacies in the usual way. Patients could modify their treatment and remain in the study. Those in the FF/VI group were allowed to change to other asthma medications and could stop taking FF/VI. Those in the usual care group were also allowed to alter medications, but could not initiate FF/VI.

Main outcome measures. The primary endpoint was ACT score at week 24 (the percentage of patients at week 24 with either an ACT score of 20 or greater or an increase of 3 or greater in the ACT score from baseline, termed responders). Safety endpoints included the incidence of serious pneumonias. The study utilized the Salford electronic medical record system, which allows near to real-time collection and monitoring of safety data. Secondary endpoints included ACT at various weeks, all asthma-related primary and secondary care contacts, annual rate of severe exacerbations, number of salbutamol inhalers dispensed, and time to modification or initial therapy.

Main results. 4233 patients were randomized, with 2119 patients randomized to usual care and 2114 randomized to the FF/VI group. 605 from the usual care group and 602 from the FF/VI group had a baseline ACT score greater than or equal to 20 and were thus excluded from the primary effectiveness analysis population. 306 in the usual care group and 342 in the FF/VI group withdrew for various reasons, including adverse events, or were lost to follow-up or protocol deviations. Mean patient age was 50 years. Within the usual care group, 64% of patients received ICS/LABA combination and 36% received ICS only. Within the FF/VI group, 65% were prescribed 100 µg/25 µg FFI/VI and 35% were prescribed 200 µg/25 µg FF/VI. At week 24, the FF/VI group had 74% responders whereas the usual care group had 60% responders; the odds of being a responder with FF/VI was twice that of being a responder with usual care (OR 1.97; 95% CI 1.71–2.26, $P < 0.001$). Patients in the FF/VI group had a slightly higher incidence of pneumonia than did the usual care group (23 vs 16; incidence ratio 1.4, 95% CI 0.8–2.7). Also, those in the FF/VI group had an increase in the rate of primary care visits/contacts per year (9.7% increase, 95% CI 4.6%–15.0%).

Conclusion. In patients with a general practitioner's diagnosis of symptomatic asthma and on maintenance inhaler therapy, initiation of a once-daily treatment regimen of combined FF/VI improved asthma control without increasing the risk of serious adverse events when compared with optimized usual care.

Commentary

Woodcock et al conducted a pragmatic randomized controlled study. This innovative research method prospectively enrolled a large number of patients who were randomized to groups that could involve 1 or more interventions and who were then followed according to the treating physician's usual practice. The patients' experience was kept as close to everyday clinical practice care as possible to preserve the real-world nature of the study. The positive aspect of this innovative pragmatic research design is the inclusion of patients with varied disease severity and with comorbidities that are not well represented in conventional double-blind randomized controlled trials, such as patients with smoking history, obesity, or multiple comorbidities. In addition, an electronic health record system was used to track serious adverse events in near real-time and increased the accuracy of the data and minimized data loss.

While the pragmatic study design offers innovation, it also has some limitations. Effectiveness studies using a pragmatic approach are less controlled compared with traditional efficacy RCTs and are more prone to low medication compliance and high rates of follow-up loss. Further, Woodcock et al allowed patients to remain in the FF/VI group even though they may have stopped taking FF/VI. Indeed, in the FF/VI group, 463 (22%) of the 2114 patients changed their medication, and 381 (18%) switched to the usual care group. Patients were analyzed using intention to treat and thus were analyzed in the group to which they were initially randomized. This could have affected results, as a good proportion of patients in the FF/VI group were not actually taking the FF/VI. Within the usual care group, 376 (18%) of 2119 patients altered their medication and 3 (< 1%) switched to FF/VI, though this was prohibited. In routine care, adherence rates are expected to be low (20%–40%) and this is another possible weakness of the study; in closely monitored RCTs, adherence rates are around 80%–90%.

The authors did not include objective measures of the severity or types of asthma, which can be obtained using pulmonary function tests, eosinophil count, or other markers of inflammation. By identifying asthma patients via the general practitioner's diagnosis, the study is more reflective of real life and primary care–driven; however, one cannot rule out accidental inclusion of patients who do not have asthma (which could include patients with post-infectious cough, vocal cord dysfunction, or anxiety) or patients who would not readily respond to typical asthma therapy (such as those with allergic bronchopulmonary aspergillosis

or eosinophilic granulomatosis with polyangitis). In addition, the authors used only subjective measures to define control: ACT score by telephone. Other outcome measures included exacerbation rate, primary care physician visits, and time to exacerbation, which may be insensitive to detecting residual inflammation or severity of asthma. In lieu of objectively measuring the degree of airway obstruction or inflammation, the outcomes measured by the authors may not have comprehensively evaluated efficacy.

The open-label, intention-to-treat, and pragmatic design of the study may have generated major selection bias, despite the randomization. Because general practitioners who directly participated in the recruitment of the patients also monitored their treatment, volunteer or referral bias may have occurred. As the authors admitted, there were differences present in practice and treatment due to variation of training and education of the general practitioners. In addition, the current study was funded by a pharmaceutical company and the trial medication was dispensed free of cost, further generating bias.

Further consideration of the study medication also brings up questions about the study design. Combined therapy with low- to moderate-dose ICS/LABA is currently indicated for asthma patients with moderate persistent or higher severity asthma. The current US insurance system encourages management to begin with low-dose ICS before escalating to a combination of ICS/LABA. Given the previously published evidence of superiority for combined ICS/LABA over ICS alone on asthma control [2,3], inclusion criteria could have been limited only to patients who were already receiving ICS/LABA to more accurately equate the trial medication with the accepted standard medications. By including patients who were on ICS/LABA as well as those only on ICS (in usual care group, 64% were on ICS/LABA and 36% were on ICS) the likelihood of responders in the FF/VI group could have been inflated compared to usual care group. In addition, patients with a low severity of asthma symptoms, such as only intermittent asthma or mild persistent asthma, could have been overtreated by FF/VI per current guidelines. About 30% of the patients initially enrolled in the study had baseline ACT scores greater than 20, and some patients had less severe asthma as indicated by the treatment with ICS alone. The authors also included 2 different doses of fluticasone furoate in their study group.

It is of concern that the incidence of pneumonia with ICS/LABA in this study was slightly higher in the FF/VI than in the usual care group. Although it was not statistically significant in this study, the increased pneumonia risk with ICS has been observed in many other studies [4,5].

Applications for Clinical Practice

Fluticasone furoate plus vilanterol (FF/VI) can be a therapeutic option in patients with asthma, with a small increased risk for pneumonia that is similar to other types of inhaled corticosteroids. However, a stepwise therapeutic approach, following the published asthma treatment strategy [6], should be emphasized when escalating treatment to include FF/VI.

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