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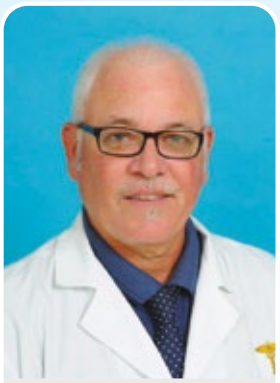

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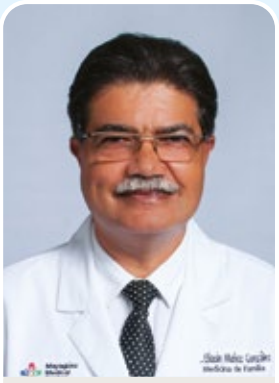

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El Grupo Hospitalario Manatí, Mayagüez, Bayamón Medical Center y Puerto Rico Women and Children's Hospital, consciente de su responsabilidad con el desarrollo de la salud en Puerto Rico, se ha convertido en pilar en la formación de los futuros médicos de la isla.

Los programas en Educación Médica en sus tres hospitales han sido reconocidos y certificados por la **Accreditation Council for Graduate Medical Education, ACGME,** al cumplir con sus rigurosos estándares de calidad para los hospitales que funcionan como centros educativos a nivel nacional. Esta acreditación es válida por 10 años y aplica a todos los programas de residencia.

Esto es otro ejemplo del compromiso del **Grupo Hospitalario** con la profesión médica, nuestra facultad, nuestros pacientes y con las comunidades a las que servimos a través de todo Puerto Rico.

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Contenido

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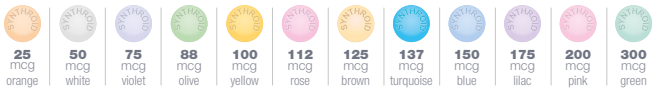
GOOD MORNING HYPOTHYROIDISM

Synthroid®
(levothyroxine sodium tablets, USP)



Tablets shown not actual size and may not represent exact color.

INDICATION[1]

Hypothyroidism

SYNTHROID® (levothyroxine sodium) tablets, for oral use is indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

Pituitary Thyrotropin (Thyroid Stimulating Hormone, TSH) Suppression
SYNTHROID is indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Limitation of Use

SYNTHROID is not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients, as there are no clinical benefits and over-treatment with SYNTHROID may induce hyperthyroidism.

SYNTHROID is not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

IMPORTANT SAFETY INFORMATION[1]

WARNING:

Thyroid hormones, including SYNTHROID, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

- SYNTHROID is contraindicated in patients with uncorrected adrenal insufficiency.
- In the elderly and in patients with cardiovascular disease, SYNTHROID should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease. If cardiac symptoms develop or worsen, the SYNTHROID dose should be reduced or withheld for one week and restarted at a lower dose.
- Patients with coronary artery disease who are receiving SYNTHROID should be monitored closely during surgical procedures for cardiac arrhythmias. Monitor patients during concomitant administration of SYNTHROID and sympathomimetic agents for signs and symptoms of coronary insufficiency.
- Use of oral thyroid hormone is not recommended in myxedema coma. Products formulated for IV administration should be used to treat myxedema coma.
- Patients with adrenal insufficiency should be treated with replacement glucocorticoids prior to initiating treatment with SYNTHROID. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated.
- SYNTHROID has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under-treatment.
- Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing SYNTHROID.
- Increased bone resorption and decreased bone mineral density may occur as a result of levothyroxine over-replacement, particularly in postmenopausal women. To mitigate this risk, patients receiving SYNTHROID should be given the minimum dose necessary that achieves the desired response.
- Adverse reactions associated with SYNTHROID therapy are primarily those of hyperthyroidism due to therapeutic overdosage.
- Many drugs and some foods affect thyroid hormone pharmacokinetics and metabolism and may alter the therapeutic response to SYNTHROID. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and actions of other drugs. Administer at least 4 hours before or after drugs that are known to interfere with absorption. Evaluate the need for dose adjustments when regularly administering within one hour of certain foods that may affect absorption. Prescribers should consult appropriate reference sources for additional information on drug or food interactions with SYNTHROID.
- SYNTHROID should not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be promptly treated. TSH levels may increase during pregnancy, so TSH should be monitored and SYNTHROID dose adjusted as needed.

Please see the following pages for brief summary of full Prescribing Information.

For more information or a copy of full Prescribing Information call AbbVie at 800-241-1643 or visit Synthroid.com.

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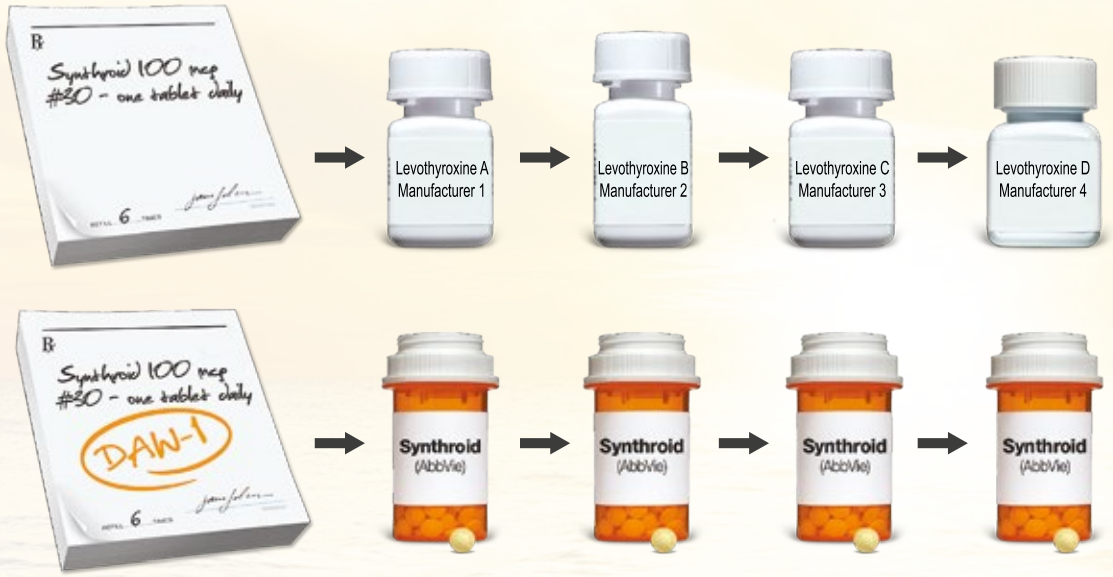
PATIENTS PRESCRIBED SYNTHROID MAY NOT ALWAYS GET SYNTHROID

37% of patients who think they are on Synthroid are actually not.†



The Food and Drug Administration (FDA) has determined that certain levothyroxine products are therapeutically equivalent. The FDA has determined that drugs that are classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the reference product.[2]

†Mistaken Generic users defined as those taking Synthroid but did not have "SYNTHROID" embossed on the pill.
A 2018 national online survey of 501 adults, diagnosed with hypothyroidism, and currently taking LT4 products.

Synthroid®

(levothyroxine sodium tablets, USP)

INDICATION[1]

Hypothyroidism

SYNTHROID® (levothyroxine sodium) tablets, for oral use is indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

Pituitary Thyrotropin (Thyroid Stimulating Hormone, TSH) Suppression SYNTHROID is indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Limitation of Use

SYNTHROID is not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients, as there are no clinical benefits and over-treatment with SYNTHROID may induce hyperthyroidism.

SYNTHROID is not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

SAFETY CONSIDERATIONS[1]

- **SYNTHROID should not be used for the treatment of obesity or for weight loss.**
- SYNTHROID is contraindicated in patients with uncorrected adrenal insufficiency.
- In the elderly and in patients with cardiovascular disease, SYNTHROID should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease. Patients with coronary artery disease who are receiving SYNTHROID should be closely monitored for cardiac arrhythmias during surgical procedures.
- Oral thyroid hormone is not recommended in myxedema coma; only products formulated for IV administration should be used.
- Patients with adrenal insufficiency should be treated with replacement glucocorticoids prior to initiating SYNTHROID.
- SYNTHROID is a narrow therapeutic index drug requiring careful titration.
- Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control. Carefully monitor glycemic control after starting, changing, or discontinuing SYNTHROID.
- Increased bone resorption and decreased bone mineral density may occur as a result of levothyroxine over-replacement, particularly in postmenopausal women.

Please see additional Important Safety Information, including BOXED Warning regarding inappropriate treatment for obesity or for weight loss, on the adjacent page.

Please see the following pages for brief summary of full prescribing information.

Reference: 1. SYNTHROID [package insert]. North Chicago, IL: AbbVie Inc. **2.** Approved Drug Products with Therapeutic Equivalence Evaluations. 39th ed. U.S. Food and Drug Administration. Available at: https:/www.fda.gov/media/71474/download. Accessed July 3, 2019.

SYNTHROID® (levothyroxine sodium tablets, USP)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

Thyroid hormones, including SYNTHROID, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss.

In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction.

Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects *[see Adverse Reactions, Drug Interactions, and Overdosage]*.

INDICATIONS AND USAGE

Hypothyroidism

SYNTHROID is indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression

SYNTHROID is indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Limitations of Use:

- SYNTHROID is not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients as there are no clinical benefits and overtreatment with SYNTHROID may induce hyperthyroidism *[see Warnings and Precautions]*.
- SYNTHROID is not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

CONTRAINDICATIONS

SYNTHROID is contraindicated in patients with uncorrected adrenal insufficiency *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Cardiac Adverse Reactions in the Elderly and in Patients with Underlying Cardiovascular Disease

Over-treatment with levothyroxine may cause an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias, particularly in patients with cardiovascular disease and in elderly patients. Initiate SYNTHROID therapy in this population at lower doses than those recommended in younger individuals or in patients without cardiac disease *[see Use in Specific Populations]*.

Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive SYNTHROID therapy. Monitor patients receiving concomitant SYNTHROID and sympathomimetic agents for signs and symptoms of coronary insufficiency.

If cardiac symptoms develop or worsen, reduce the SYNTHROID dose or withhold for one week and restart at a lower dose.

Myxedema Coma

Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Use of oral thyroid hormone drug products is not recommended to treat myxedema coma. Administer thyroid hormone products formulated for intravenous administration to treat myxedema coma.

Acute Adrenal Crisis in Patients with Concomitant Adrenal Insufficiency

Thyroid hormone increases metabolic clearance of glucocorticoids. Initiation of thyroid hormone therapy prior to initiating glucocorticoid therapy may precipitate an acute adrenal crisis in patients with adrenal insufficiency. Treat patients with adrenal insufficiency with replacement glucocorticoids prior to initiating treatment with SYNTHROID *[see Contraindications]*.

Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

SYNTHROID has a narrow therapeutic index. Over- or undertreatment with SYNTHROID may have negative effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and glucose and lipid metabolism. Titrate the dose of SYNTHROID carefully and monitor response to titration to avoid these effects. Monitor for the presence of drug or food interactions when using SYNTHROID and adjust the dose as necessary *[see Drug Interactions]*.

Worsening of Diabetic Control

Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing SYNTHROID *[see Drug Interactions]*.

Decreased Bone Mineral Density Associated with Thyroid Hormone Over-Replacement

Increased bone resorption and decreased bone mineral density may occur as a result of levothyroxine over-replacement, particularly in post-menopausal women. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase, and suppressed serum parathyroid hormone levels. Administer the minimum dose of SYNTHROID that achieves the desired clinical and biochemical response to mitigate this risk.

ADVERSE REACTIONS

Adverse reactions associated with SYNTHROID therapy are primarily those of hyperthyroidism due to therapeutic overdosage *[see Warnings and Precautions* and *Overdosage]*. They include the following:

- *General:* fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating
- *Central nervous system:* headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia
- *Musculoskeletal:* tremors, muscle weakness, muscle spasm
- *Cardiovascular:* palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest
- *Respiratory:* dyspnea
- *Gastrointestinal:* diarrhea, vomiting, abdominal cramps, elevations in liver function tests
- *Dermatologic:* hair loss, flushing, rash
- *Endocrine:* decreased bone mineral density
- *Reproductive:* menstrual irregularities, impaired fertility

Seizures have been reported rarely with the institution of levothyroxine therapy.

Adverse Reactions in Children

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Hypersensitivity Reactions

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various gastrointestinal symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness, and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

DRUG INTERACTIONS

Drugs Known to Affect Thyroid Hormone Pharmacokinetics

Many drugs can exert effects on thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to SYNTHROID (see Tables 1-4 below).

Table 1. Drugs That May Decrease T4 Absorption (Hypothyroidism)

Potential impact: Concurrent use may reduce the efficacy of SYNTHROID by binding and delaying or preventing absorption, potentially resulting in hypothyroidism.	
Drug or Drug Class	**Effect**
Calcium Carbonate Ferrous Sulfate	Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer SYNTHROID at least 4 hours apart from these agents.
Orlistat	Monitor patients treated concomitantly with orlistat and SYNTHROID for changes in thyroid function.
Bile Acid Sequestrants - Colesevelam - Cholestyramine - Colestipol Ion Exchange Resins - Kayexalate - Sevelamer	Bile acid sequestrants and ion exchange resins are known to decrease levothyroxine absorption. Administer SYNTHROID at least 4 hours prior to these drugs or monitor TSH levels.
Other drugs: Proton Pump Inhibitors Sucralfate Antacids - Aluminum & Magnesium Hydroxides - Simethicone	Gastric acidity is an essential requirement for adequate absorption of levothyroxine. Sucralfate, antacids and proton pump inhibitors may cause hypochlorhydria, affect intragastric pH, and reduce levothyroxine absorption. Monitor patients appropriately.

Table 2. Drugs That May Alter T4 and Triiodothyronine (T3) Serum Transport Without Affecting Free Thyroxine (FT4) Concentration (Euthyroidism)

Drug or Drug Class	**Effect**
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	These drugs may increase serum thyroxine-binding globulin (TBG) concentration.
Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.
Potential impact (below): Administration of these agents with SYNTHROID results in an initial transient increase in FT4. Continued administration results in a decrease in serum T4 and normal FT4 and TSH concentrations.	
Salicylates (> 2 g/day)	Salicylates inhibit binding of T4 and T3 to TBG and transthyretin. An initial increase in serum FT4 is followed by return of FT4 to normal levels with sustained therapeutic serum salicylate concentrations, although total T4 levels may decrease by as much as 30%.
Other drugs: Carbamazepine Furosemide (> 80 mg IV) Heparin Hydantoins Non-Steroidal Anti-inflammatory Drugs - Fenamates	These drugs may cause protein-binding site displacement. Furosemide has been shown to inhibit the protein binding of T4 to TBG and albumin, causing an increase free T4 fraction in serum. Furosemide competes for T4-binding sites on TBG, prealbumin, and albumin, so that a single high dose can acutely lower the total T4 level. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total and free T4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid. Closely monitor thyroid hormone parameters.

Table 3. Drugs That May Alter Hepatic Metabolism of T4 (Hypothyroidism)

Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased SYNTHROID requirements.	
Drug or Drug Class	**Effect**
Phenobarbital Rifampin	Phenobarbital has been shown to reduce the response to thyroxine. Phenobarbital increases L-thyroxine metabolism by inducing uridine 5'-diphospho-glucuronosyltransferase (UGT) and leads to a lower T4 serum levels. Changes in thyroid status may occur if barbiturates are added or withdrawn from patients being treated for hypothyroidism. Rifampin has been shown to accelerate the metabolism of levothyroxine.

Table 4. Drugs That May Decrease Conversion of T4 to T3

Potential impact: Administration of these enzyme inhibitors decreases the peripheral conversion of T4 to T3, leading to decreased T3 levels. However, serum T4 levels are usually normal but may occasionally be slightly increased.	
Drug or Drug Class	**Effect**
Beta-adrenergic antagonists (e.g., Propranolol > 160 mg/day)	In patients treated with large doses of propranolol (> 160 mg/day), T3 and T4 levels change, TSH levels remain normal, and patients are clinically euthyroid. Actions of particular beta-adrenergic antagonists may be impaired when a hypothyroid patient is converted to the euthyroid state.
Glucocorticoids (e.g., Dexamethasone ≥ 4 mg/day)	Short-term administration of large doses of glucocorticoids may decrease serum T3 concentrations by 30% with minimal change in serum T4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T3 and T4 levels due to decreased TBG production (See above).
Other drugs: Amiodarone	Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, and decreased or normal free-T3) in clinically euthyroid patients.

Antidiabetic Therapy

Addition of SYNTHROID therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control, especially when thyroid therapy is started, changed, or discontinued *[see Warnings and Precautions]*.

Oral Anticoagulants

SYNTHROID increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the SYNTHROID dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

Digitalis Glycosides

SYNTHROID may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may decrease when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides.

Antidepressant Therapy

Concurrent use of tricyclic (e.g., amitriptyline) or tetracyclic (e.g., maprotiline) antidepressants and SYNTHROID may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and central nervous system stimulation. SYNTHROID may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on SYNTHROID may result in increased SYNTHROID requirements.

Ketamine

Concurrent use of ketamine and SYNTHROID may produce marked hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients.

Sympathomimetics

Concurrent use of sympathomimetics and SYNTHROID may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.

Tyrosine-Kinase Inhibitors

Concurrent use of tyrosine-kinase inhibitors such as imatinib may cause hypothyroidism. Closely monitor TSH levels in such patients.

Drug-Food Interactions

Consumption of certain foods may affect SYNTHROID absorption thereby necessitating adjustments in dosing. Soybean flour, cottonseed meal, walnuts, and dietary fiber may bind and decrease the absorption of SYNTHROID from the gastrointestinal tract. Grapefruit juice may delay the absorption of levothyroxine and reduce its bioavailability.

Drug-Laboratory Test Interactions

Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone and/or determine the free-T4 index (FT4I) in this circumstance. Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentration. Nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, androgens, and corticosteroids decrease TBG concentration. Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Experience with levothyroxine use in pregnant women, including data from post-marketing studies, have not reported increased rates of major birth defects or miscarriages *[see Data]*. There are risks to the mother and fetus associated with untreated hypothyroidism in pregnancy. Since TSH levels may increase during pregnancy, TSH should be monitored and SYNTHROID dosage adjusted during pregnancy *[see Clinical Considerations]*. There are no animal studies conducted with levothyroxine during pregnancy. SYNTHROID should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Maternal hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, gestational hypertension, pre-eclampsia, stillbirth, and premature delivery. Untreated maternal hypothyroidism may have an adverse effect on fetal neurocognitive development.

Dose Adjustments During Pregnancy and the Postpartum Period

Pregnancy may increase SYNTHROID requirements. Serum TSH levels should be monitored and the SYNTHROID dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the SYNTHROID dosage should return to the pre-pregnancy dose immediately after delivery *[see Dosage and Administration]*.

Data

Human Data

Levothyroxine is approved for use as a replacement therapy for hypothyroidism. There is a long experience of levothyroxine use in pregnant women, including data from post-marketing studies that have not reported increased rates of fetal malformations, miscarriages or other adverse maternal or fetal outcomes associated with levothyroxine use in pregnant women.

Lactation

Risk Summary

Limited published studies report that levothyroxine is present in human milk. However, there is insufficient information to determine the effects of levothyroxine on the breastfed infant and no available information on the effects of levothyroxine on milk production. Adequate levothyroxine treatment during lactation may normalize milk production in hypothyroid lactating mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SYNTHROID and any potential adverse effects on the breastfed infant from SYNTHROID or from the underlying maternal condition.

Pediatric Use

The initial dose of SYNTHROID varies with age and body weight. Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters.

In children in whom a diagnosis of permanent hypothyroidism has not been established, discontinue SYNTHROID administration for a trial period, but only after the child is at least 3 years of age. Obtain serum T4 and TSH levels at the end of the trial period, and use laboratory test results and clinical assessment to guide diagnosis and treatment, if warranted.

Congenital Hypothyroidism

Rapid restoration of normal serum T4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, initiate SYNTHROID therapy immediately upon diagnosis. Levothyroxine is generally continued for life in these patients.

Closely monitor infants during the first 2 weeks of SYNTHROID therapy for cardiac overload, arrhythmias, and aspiration from avid suckling.

Closely monitor patients to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment is associated with craniosynostosis in infants, may adversely affect the tempo of brain maturation, and may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Acquired Hypothyroidism in Pediatric Patients

Closely monitor patients to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

Geriatric Use

Because of the increased prevalence of cardiovascular disease among the elderly, initiate SYNTHROID at less than the full replacement dose *[see Warnings and Precautions]*. Atrial arrhythmias can occur in elderly patients. Atrial fibrillation is the most common of the arrhythmias observed with levothyroxine overtreatment in the elderly.

OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism *[see Warnings and Precautions* and *Adverse Reactions]*. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures occurred in a 3-year-old child ingesting 3.6 mg of levothyroxine. Symptoms may not necessarily be evident or may not appear until several days after ingestion of levothyroxine sodium.

Reduce the SYNTHROID dose or discontinue temporarily if signs or symptoms of overdosage occur. Initiate appropriate supportive treatment as dictated by the patient's medical status.

For current information on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

PATIENT COUNSELING INFORMATION

Inform the patient of the following information to aid in the safe and effective use of *SYNTHROID:*

Dosing and Administration

- Instruct patients to take SYNTHROID only as directed by their healthcare provider.
- Instruct patients to take SYNTHROID as a single dose, preferably on an empty stomach, one-half to one hour before breakfast.
- Inform patients that agents such as iron and calcium supplements and antacids can decrease the absorption of levothyroxine. Instruct patients not to take SYNTHROID tablets within 4 hours of these agents.
- Instruct patients to notify their healthcare provider if they are pregnant or breastfeeding or are thinking of becoming pregnant while taking SYNTHROID.

Important Information

- Inform patients that it may take several weeks before they notice an improvement in symptoms.
- Inform patients that the levothyroxine in SYNTHROID is intended to replace a hormone that is normally produced by the thyroid gland. Generally, replacement therapy is to be taken for life.
- Inform patients that SYNTHROID should not be used as a primary or adjunctive therapy in a weight control program.
- Instruct patients to notify their healthcare provider if they are taking any other medications, including prescription and over-the-counter preparations.
- Instruct patients to notify their physician of any other medical conditions they may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems, as the dose of medications used to control these other conditions may need to be adjusted while they are taking SYNTHROID. If they have diabetes, instruct patients to monitor their blood and/or urinary glucose levels as directed by their physician and immediately report any changes to their physician. If patients are taking anticoagulants, their clotting status should be checked frequently.
- Instruct patients to notify their physician or dentist that they are taking SYNTHROID prior to any surgery.

Adverse Reactions

- Instruct patients to notify their healthcare provider if they experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, heat intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.
- Inform patients that partial hair loss may occur rarely during the first few months of SYNTHROID therapy, but this is usually temporary.

AbbVie Inc.
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Los retos y las oportunidades de mejorar

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Los retos –llámense problemas, inconvenientes, objetivos que parecen inalcanzables, o situaciones difíciles y de incertidumbre– son parte de la vida. Ellos nos ayudan a ser mejores, a descubrir cosas nuevas y a progresar. En el camino podremos cometer equivocaciones y fallar muchas veces, ya que las soluciones a los grandes retos no suelen ser inmediatas. Por otro lado, teniendo preparación, práctica y –sobre todo– voluntad, la probabilidad de resolver un reto será mucho mayor.

Cuando aprendimos a caminar, nos tropezamos muchas veces; cuando fuimos a la escuela, los maestros trataron de corregir nuestros errores; cuando estudiamos una profesión, tuvimos que avanzar por etapas, paso a paso. Aprender toma tiempo. No es sencillo atender a un paciente en una unidad de cuidados intensivos, decidir sobre un tratamiento oncológico, interpretar unas imágenes radiológicas complejas ni hacer alguna cirugía. El aprendizaje, el estudio, la práctica y la experiencia van mejorando poco a poco nuestras capacidades, habilidades o destrezas. Para eso, se requieren la voluntad de aprender y la tenacidad de pasar por distintas etapas. Esto ocurre en todos los oficios, profesiones, actividades y campos donde nos toque desempeñarnos. Indudablemente, a ello se debe sumar los valores y principios, que son los que dan solidez a todo lo que hacemos.

A nivel de la sociedad también surgen retos importantes. Nos ha tocado empezar esta década en Puerto Rico con una crisis por movimientos sísmicos, que se viene a sumar a problemas pendientes originados por los huracanes de 2017 y a situaciones administrativas complejas. A todo esto se agrega ahora una nueva pandemia viral. Estas circunstancias requieren muchas veces de una respuesta individual, ya que nos afectan o comprometen directa o indirectamente.

Ante los retos debemos mantener la entereza, la empatía y, en especial, tener claros nuestros objetivos para, con energía y paciencia, seguir el camino e ir sorteando obstáculos y así poder alcanzar nuestras metas. En este sentido, cabe mencionar aquí dos frases clásicas: "El único hombre que no se equivoca es el que no hace nada" y "El mayor de los errores es no hacer nada".

En este número de *Galenus* incluimos artículos sobre temas importantes en los que se presentan avances en distintos campos médicos, así como información que esperamos disfruten y les sea de utilidad, ya que se trata de material que ha sido preparado con el objetivo que nos acompaña siempre, que es el de compartir para progresar.

¡Saludos, amigos!

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En Auxilio Mutuo facilitamos el acceso a los servicios del Centro de Trasplante, con Clínicas Satélites en **Ponce, Aguadilla, San Germán y Fajardo,** donde ofrecemos orientación sobre el proceso de trasplante de riñón y páncreas, y servicios de evaluación para pacientes adultos, incluyendo trasplantes de donantes vivos.

Porque al momento de un trasplante, estar cerca de la familia, no tiene precio.

El Centro de Trasplante es la única facilidad en Puerto Rico y en el Caribe que ostenta la aprobación de "United Network for Organ Sharing" (UNOS) para el Programa de Trasplante de Riñón, el Programa de Trasplante de Riñón-Páncreas y el Programa de Trasplante de Hígado.

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Inmunoterapia en cáncer:
Beneficios y riesgos del tratamiento

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Introducción

La *inmunoncología* estudia cómo nuestro sistema inmune interacciona frente a las células malignas. Se conoce como *inmunovigilancia* al proceso de controlar y destruir –de ser necesario– las células cancerosas que se forman en nuestro organismo. Recientemente, se ha encontrado que muchas veces el sistema inmune actúa como inmunomodificador a través de receptores y/o citoquinas para hacer más vulnerables a estas células malignas que han perdido los controles normales.

Algunos de los mecanismos de control inmune más importantes que se conocen en la actualidad son los siguientes:

- CTLA-4: antígeno 4 del linfocito T citotóxico. Este receptor está presente en las células T y controla su activación. Las células malignas pueden manipular este receptor para escapar de la vigilancia;

- PD-L1: el ligando 1 de muerte celular programada (PD-L1) es una proteína transmembrana de tipo 1 que juega un rol inmunoregulador mediante la supresión del sistema inmune en procesos fisiológicos como el embarazo, la presentación de antígenos a linfocitos T, el trasplante de órganos y también en procesos patológicos, como en las enfermedades inmunológicas, en el cáncer y en las enfermedades infecciosas;

- Tim3: receptor 3 inhibidor de dominio de mucina de los linfocitos T. Controla la función del linfocito T4 ayudante; y

- Lag3: gen activador de linfocitos que puede inducir anergia linfocitaria. Las células malignas lo pueden inhibir.

Las células malignas utilizan mecanismos para escapar del sistema inmune. Los mecanismos que utilizan son múltiples. Algunos de estos son los siguientes:

1. Alteración de proteínas antigénicas;
2. Manipulación de citoquinas; y
3. Activación de moléculas de punto del control inmune.

Estas alteraciones dificultan establecer una respuesta adecuada contra estas células, escapándose entonces de los controles normales y produciendo la enfermedad.

Conociendo estos mecanismos de escape, se ha logrado desarrollar múltiples terapias para restablecer los controles normales y destruir las células malignas. Estas incluyen las siguientes opciones:

Citoquinas

1. Interleucina 2: citoquina que activa los linfocitos T. Se usa para tratar melanoma y tumores renales;
2. Lenalidomida/pomalidomida: inmunomodulador, en tratamiento de mieloma múltiple y de linfomas;
3. Interferón alfa: inactiva proteínas STAT 1, 2, en tratamiento de melanoma; y
4. BCG: inductor de citoquinas y en la activación de linfocitos, de aplicación en cáncer de vejiga.

Inhibidores de punto

Son anticuerpos monoclonales contra el ligando 1 de muerte celular programada (PD-L1). El bloqueo de PD-L1 revierte el agotamiento de las células T revitalizando la actividad antitumoral. Estos agentes son activos en múltiples tumores. Pueden trabajar como agentes sencillos o en combinación. La lista de agentes incluye: nivolumab (*Opdivo*), pembrolizumab (*Keytruda*), cemiplimab (*Libtayo*), durvalumab (*Infinzi*), avelumab (*Bavencio*) y atezolizumab (*Tecentriq*). Envafolimab es un inibidor del PD-L1 subcutáneo que está bajo estudio, muy activo contra varios tumores.

CTLA-4

Receptor que puede ser inhibido; ipilimumab es un anticuerpo monoclonal activo contra el melanoma, los tumores de pulmón y los tumores renales.

Receptor de antígeno quimérico (CAR-T)

Infusión de linfocitos manipulados que tiene indicación en linfomas y leucemias agudas (*Tisagenlecleucel –Kymriah–*).

Terapia dirigida contra CD3

Activador bioespecífico de células T, blinatumomab (*Blincyto*). Activo en leucemia linfoblástica aguda.

Virus oncolíticos

Entre estos, destaca la terapia contra el melanoma cutáneo por manipulación de los virus de herpes (Talimogene laherparepvec o T-VEC).

Vacunas

Se han desarrollado vacunas utilizando antígenos tumorales a través de ingeniería genética. Así, se dispone de sipuleucel-T que tiene indicación para tratar cáncer de próstata avanzado.

Se viene estudiando también el uso de anticuerpos contra los receptores de las células asesinas (*Natural Killer Cells*), la infusión de macrófagos infiltrantes de tumor y, además, la expresión de la enzima deoxigenasa 2,3 de indo-lámina puede manipularse para permitir que los inhibidores de PD-L1 recuperen su activad (mecanismo de resistencia).

Criterios de respuesta de la enfermedad

Se han modificado los criterios de respuesta de la enfermedad oncológica al usar inmunoterapia. Los cambios más importantes incluyen:

1. El paciente puede tener un periodo de deterioro de la enfermedad al inicio del tratamiento. Esto se conoce como pseudoprogresión;
2. La respuesta de la enfermedad puede tomar más tiempo en observarse, a veces meses; y
3. La enfermedad puede no presentar respuesta objetiva por estudios de imágenes, pero el paciente puede presentar mejoría clínica.

La mayor diferencia que se describe para evaluar la respuesta al tratamiento es el término *progresión no confirmada*: puede aparecer una lesión nueva, y se debe esperar hasta la próxima reevaluación para determinar si aparecen más lesiones y confirmar la progresión de la enfermedad, dentro de las próximas 12 semanas.

Hiperprogresión de la malignidad

La hiperprogresión de la malignidad en pacientes de cáncer tratados con inmunoterapia se ha descrito en un 4% a un 29% de los casos, en su mayoría tratados por tumores de pulmón. Esta se define como un crecimiento rápido de la enfermedad en los pacientes que se encuentran en tratamiento.

Es importante tener un alto grado de sospecha acerca de cuándo debe detenerse el tratamiento. El pronóstico de estos pacientes tiende a ser pobre. Hasta ahora no se ha podido identificar alguna característica en especial que pueda predecir qué pacientes están a riesgo.

Efectos secundarios de la inmunoterapia

Los efectos secundarios asociados a la inmunoterapia y a los inhibidores de punto son variados.

En general, si el efecto secundario es leve, se puede manejar con un curso corto de corticoesteroides y parar el tratamiento por un tiempo corto.

En caso de eventos adversos severos, se deben usar altas dosis de corticoesteroides, detener el medicamento y considerar administrar infliximab (*Remicade*).

Los efectos secundarios más comunes incluyen:

Efecto secundario	Características y manejo
Fatiga	Ocurre en el 16% al 24% de los casos. Usualmente es leve. Raras veces requiere tratamiento.
Reacciones durante la infusión del agente	Puede ocurrir hasta en un 25% de los casos. No requiere premedicación. Casos severos podrían necesitar premedicación para los próximos tratamientos.
Toxicidad dermatológica	Puede ocurrir hasta en un 50% de los casos. Usualmente la toxicidad es leve, pero podrían necesitar esteroides y descontinuar el medicamento.
Diarreas, colitis y hepatotoxicidad	Muy frecuente. Usualmente comienza luego de las primeras 6 semanas de tratamiento. Se puede usar loperamide. Los casos severos necesitan esteroides y descontinuar el medicamento. La hepatotoxicidad puede comenzar luego de 8 a 12 semanas y podría ser severa. Pueden usarse esteroides y micofenolato.
Neumonitis	Ocurre hasta en un 5% de los casos. Se ha descrito hasta 2.8 meses después de empezar el tratamiento. Casos severos necesitan esteroides y descontinuar el medicamento.
Endocrinopatías	Frecuente. Puede afectar la glándula tiroides (común), adrenales y pituitaria. Podría requerir suplemento de la hormona afectada.

Otros efectos secundarios menos frecuentes son los siguientes: Daño renal, pancreatitis, toxicidad cardiovascular, toxicidad neurológica (Guillan-Barre, miastenia gravis), toxicidad a la visión, problemas hematológicos y daño reumatológico o musculoesquelético.

Resumen

La inmunooncología es un área médica que ha tenido avances extraordinarios que se han traducido en un gran beneficio a los pacientes. Siendo la inmunoterapia un método de tratamiento activo para una extensa gama de tumores, debemos familiarizarnos con su manejo y espectro de eventos adversos.

También, debemos estar atentos a la nueva información disponible y a los adelantos que van surgiendo y que contribuyen al beneficio de nuestros pacientes que son nuestra razón de ser.

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Cardiomiopatía diabética:

Últimos avances en su tratamiento

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Ex Presidente de la Sociedad Puertorriqueña
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La diabetes mellitus causa cardiopatía y fallo cardiaco congestivo de forma independiente a la presencia de hipertensión arterial y/o de enfermedad coronaria. A esta condición se le denomina cardiomiopatía diabética y ya se le reconoce como una entidad clínica de importancia en nuestros pacientes afectados por diabetes.

Mecanismo y evolución clínica

Recientemente se han presentado resultados de múltiples investigaciones científicas tratando de explicar los mecanismos moleculares, estructurales y funcionales, de tal manera que se puedan desarrollar estrategias efectivas para la prevención y el tratamiento de esta complicación.

Según el estudio de Framingham, la presencia de diabetes aumenta el riesgo de fallo cardiaco:[1]

- 2 veces más en varones diabéticos;
- 5 veces más en mujeres diabéticas;
- 4 veces más en varones sobre los 65 años; y
- 8 veces más en mujeres jóvenes diabéticas.

Según el estudio de prevalencia US HMO:[2]

- Con diabetes la incidencia de fallo cardiaco aumenta en un índice de 3.3% anual

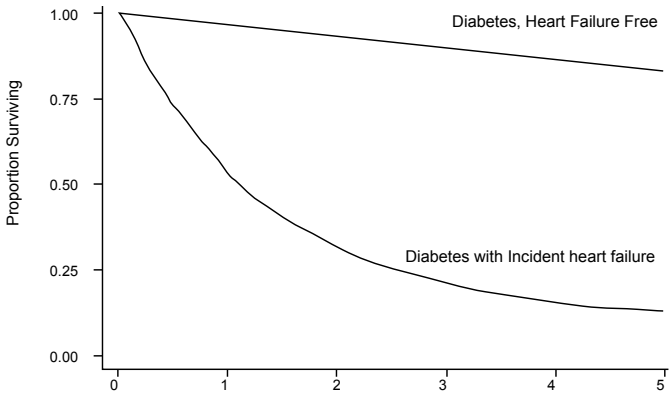
La relación entre la diabetes mellitus y la enfermedad cardiovascular es un hecho establecido. Ya varios estudios epidemiológicos confirman la relación entre la diabetes mellitus y el fallo cardiaco congestivo.

Los cambios estructurales del miocardio que se describen en el paciente diabético eventualmente resultan en una disfunción ventricular, con aumento en el grosor de la pared y de la masa del ventrículo izquierdo.

Inicialmente hay una etapa subclínica que se manifiesta en la incapacidad del ventrículo izquierdo a relajarse en forma apropiada. En esta fase el paciente está asintomático y los síntomas clínicos típicos del fallo cardiaco congestivo se van desarrollando en forma progresiva. Los cambios estructurales del ventrículo izquierdo resultan en una incapacidad para que el mismo pueda completar su llenado (relleno ventricular izquierdo), causando esto una disfunción diastólica, la cual precede a la disfunción sistólica del ventrículo.

Muchos de estos pacientes evolucionan de la fase subclínica a la fase de fallo congestivo con una fracción de eyección preservada (HFpEF), y eventualmente a fallo cardiaco con una fracción de eyección reducida (HFrEF).

La mortalidad de esta población es relativamente alta:[4]



Aspectos patofisiológicos

La patofisiología de esta condición es multifactorial ya que se encuentran involucrados cambios en el metabolismo de los ácidos grasos, una hiperglucemia crónica, cambios inducidos en las hormonas circulantes y en las citocinas.

En la cardiomiopatía diabética la contractilidad del miocito cardiaco se afecta por la alteración en las señales de insulina que reducen la capacidad de captar glucosa resultando en el aumento intracelular de iones de calcio, afectando así la dinámica de la contracción/relajación del miocito.

Además, hay cambios oxidativos con alteraciones en la oxidación de ácidos grasos a nivel mitocondrial, el rol de TGF-β (*transformin growth factor beta*) está activo en la fibrosis muscular, hay procesos inflamatorios y acumulación de productos de glicación avanzada (AGE), entre otros.

Opciones terapéuticas

Los nuevos fármacos que inhiben el cotransportador de sodio/glucosa a nivel del túbulo renal (*SGLT2 inhibitors*) han tenido un efecto beneficioso en el paciente diabético con fallo cardiaco congestivo. El tratamiento con estos nuevos fármacos SGLT2 ha cobrado una importancia enorme en el enfoque terapéutico del paciente diabético tipo 2 que además está complicado con fallo cardiaco.

Las nuevas guías de la Asociación Americana de Diabetes indican que un paciente diabético tipo 2 con manifestaciones de fallo cardiaco debe ser tratado con uno de estos agentes, que tenga evidencia de efectividad en el caso específico.

¿Es este un efecto de clase?[5]
¿Qué ocurre en el mundo real?
Información acumulada en 6 países sobre datos en 309,056 pacientes con diabetes mellitus tipo 2:

- El tratamiento con inhibidores de SGLT2 (dapagliflozina, canagliflozina y empagliflozina) se asocia a un 39% de reducción en el número de hospitalizaciones por fallo cardiaco;
- Las disminuciones en muertes son similares por todas las causas.

Comentario

No hay duda de que los endocrinólogos, cardiólogos y nefrólogos van a tener que trabajar en equipo junto al médico primario para educar, tratar e impactar positivamente a la población afectada con diabetes mellitus y con compromiso cardiaco.

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El programa CANVAS incorporó a 10,142 participantes; 1461 (14.4%) con historia de fallo cardiaco basal[5]:
Información acumulada en 6 países sobre datos en 309,056 pacientes con diabetes mellitus tipo 2:

- Reducción de muertes por causa cardiovascular u hospitalización por fallo cardiaco en pacientes tratados con canagliflozin comparado con placebo (16.3 vs 20.8 por 1000 pacientes/año, HR=0.78 (95% CI: 0.67, 0.91);
- Reducción de fallo cardiaco fatal o con hospitalización por fallo cardiaco (HR=0.70 [95% CI: 0.55, 0.89]) y de fallo cardiaco solo con hospitalización en (HR=0.67 [95% CI: 0.52, 0.87]);
- El beneficio sobre las muertes cardiovasculares u hospitalizaciones por fallo cardiaco puede ser mayor en pacientes con historia previa de fallo cardiaco (HR=0.61 [95% CI: 0.46, 0.80]) comparado con pacientes sin fallo cardiaco basal (HR=0.87 [95% CI: 0.72, 1.06]); P interacción=.021).

In HR+, HER2- MBC

A SIGNIFICANT SURVIVAL IMPROVEMENT

With consistent results even in women likely to do worse[1-6]*

Verzenio + fulvestrant helps to raise the bar of what is possible for pre/peri- and postmenopausal women with disease recurrence or progression following endocrine therapy (ET)

46.7-month mOS with Verzenio + fulvestrant (n=446) (95% CI: 39.2-52.2) vs **37.3-month** mOS with fulvestrant alone (n=223) (95% CI: 34.4-43.2); **HR=0.757** (95% CI: 0.606-0.945), ***P*=.0137**[2,7]

*Visceral disease and primary ET resistance were studied in the clinical trial and could confer a less favorable prognosis. For more information on trial design, see below.

MONARCH 2 was a phase III, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2− MBC who progressed on or after ET. Pre/perimenopausal women (17%) were rendered postmenopausal prior to the study. Patients had received no chemotherapy and no more than 1 prior ET in the metastatic setting. Patients were randomized 2:1 to Verzenio + fulvestrant (n=446) or placebo + fulvestrant (n=223). Verzenio and placebo were dosed PO BID on a continuous dosing schedule until disease progression or unacceptable toxicity. 500 mg fulvestrant was administered by IM injection on days 1, 15, and 29 of the first month and once monthly thereafter. The primary endpoint was PFS. Key secondary endpoints were ORR, OS, and DoR.[1,8]

BID=twice a day; CI=confidence interval; DoR=duration of response; HR=hazard ratio; IM=intramuscular; mOS=median overall survival; ORR=objective response rate; OS=overall survival; PO=orally; PFS=progression-free survival.

Verzenio is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced or metastatic breast cancer (MBC)[1]:

- In **combination with fulvestrant** for women with disease progression following endocrine therapy

SELECT IMPORTANT SAFETY INFORMATION

Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.

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