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News and Information for West Virginia Providers from the West Virginia Bureau for Medical Services (WVBMS)

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June 2017
Published Quarterly by Health Information Designs, LLC

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Topics Covered in This Issue

Biologic Agents for the Treatment of Rheumatoid Arthritis (RA)

Introduction

- Biologic agents offer a great next line of therapy for patients who fail treatment with the conventional disease-modifying antirheumatic drugs (DMARDs).
- The biologics are genetically engineered proteins originating from human genes. They are very beneficial in treating RA due to their ability to target specific parts of the immune system that fuel inflammation. The conventional DMARDs do not act so specifically.
- Biologic agents have different mechanisms in which they reduce inflammation and slow RA progression. These include the following:
  - Block proinflammatory cytokines
    - TNF-α inhibitor (infliximab, etanercept, adalimumab, golimumab, and certolizumab)
    - IL-1 receptor antagonist (anakinra)

        - IL-6 receptor antagonist (tocilizumab)
    - Deplete peripheral B cells (rituximab)
    - Bind to CD80/86 on T cells to prevent the costimulation needed to fully activate T cells (abatacept)

Role in Therapy

- Biologic agents are considered after conventional DMARDs fail to achieve adequate responses. These agents are considerably more expensive which is one of the reasons for them being considered second-line. Biologics may be used alone or in combination with methotrexate or other nonbiologic DMARDs.
- RA treatment with a biologic agent will reduce the signs/symptoms, induce major clinical response, inhibit progression of structural damage, and improve physical function.

Benefits and Risks

- The greatest benefit with using biologic agents is their ability to target a specific part of the immune system. They are very effective in reducing inflammation and suspending disease progression. They may also work better at controlling symptoms than older RA medications.
- The benefit of targeting the immune system can also be considered a risk. With using biologic agents, part of the immune system is essentially turned off. This can lead to an increased risk of serious infections.

Safety

- There have been concerns brought about that biologic agents treating RA may increase the risk of cancer. The concern came from the theory that with tampering down the immune system, the agents also decreased the body's ability to protect against cancer. This was especially thought to be true with inhibiting tumor necrosis factor, a molecule that conducts immunosurveillance of tumors. However, growing evidence show that biologics are not associated with an increased risk of malignancies.
- Early studies suggested that biologic agents caused up to a three-fold increase for developing cancer, particularly lymphomas. However, more recent research, including a 2016 study involving more than 15,000 RA patients, found no increased risk for lymphoma. Now it is thought that the chronic inflammation itself is the primary link to cancer and not the medications themselves. The two main lymphocytes, B cells and T cells, involved in the inflammation with RA are the same cells that become cancerous in lymphomas. Patients that have the most poorly controlled inflammation are at the highest risk of developing lymphomas.
- Other safety concerns include the following:
    - Reactivation of Latent Tuberculosis (TB)
        - There has been an association of reactivation of latent TB with patients being treated with TNF inhibitors. However, the incidence of TB is also seen at an increased rate with RA patients without this agent. It is still recommended to be screened for TB prior to being initiated on biologic therapy.
    - Hepatitis Reactivation
        - A history of hepatitis B or C should be considered before initiating a biologic due to a risk of hepatitis reactivation.

- Future Vaccinations
  - Live vaccines are not recommended during treatment with any biologic agent.
- Future Surgery
  - Due to their ability to dampen the immune system and risk of infection, biologic treatment should be either postponed or suspended if surgery is required.
- Use During Pregnancy
  - There are currently no long-term studies with most biologics to determine their safety for fetuses and infants.

Recommendations

- Biologic agents are recommended as second-line therapy after the conventional DMARDs. Before starting a biologic considerations should be taken with respect to current infections, history of TB, history of hepatitis B or C, history of cancer, future vaccinations and surgeries, and also if the patient is planning to become pregnant.
- Overall, biologic agents have been proven to be very effective for RA and should be considered as alternate therapies in these patients.

FDA Drug Safety Announcement: Restricting Use of Codeine and Tramadol in Children

Introduction

- The Food and Drug Administration (FDA) has issued new warnings on the use of codeine and tramadol in children and breastfeeding women
- The FDA used data from its FDA Adverse Event Reporting System from 1969 to 2015 to identify cases of fatal or life-threatening respiratory depression in pediatric and adolescent patients after the use of codeine or tramadol containing products.
- This data was used to establish the need for new warnings of the increased risk of respiratory depression and death with codeine and tramadol in certain patient groups.
- Also, the FDA reviewed medical literature to determine that breastfed infants could be inadvertently exposed to codeine, tramadol and their active metabolites if the mothers had taken the medication.

Codeine

- Codeine is a controlled substance used to treat pain or cough in adults.
- Codeine can be used alone or in combination with many other medications to treat these indications.
- Small amounts of codeine are metabolized by the cytochrome p450 enzyme 2D6 to morphine, which activates opioid receptors in the central nervous system.
- Opiate receptor activation causes generalized central nervous system depression, and inhibition of the ascending pain pathway causing a decreased perception of pain.

- Also, opiate receptor activation in the medulla causes respiratory depression, which is useful to suppress cough symptoms.
- Some patients have a genetic polymorphism which causes the increased metabolism of codeine into morphine, and can cause unintentionally high levels of morphine in these patients leading to significant respiratory depression and even death.
- Codeine's active metabolite, morphine, is excreted in the breastmilk of nursing mothers.
- The concentrations present in the breastmilk are dependent upon dose and the mother's metabolism of codeine.

Tramadol

- Tramadol is also a controlled substance used to treat moderate to severe pain in adults.
- Tramadol is a synthetic form of codeine and has a weaker affinity for the opioid receptor than codeine.
- Therefore, tramadol generally has less abuse potential and respiratory depression than codeine.
- Tramadol also has a secondary mechanism by which it inhibits the reuptake of norepinephrine and serotonin in the brain, which aids in its ability to treat pain.
- The blockade of norepinephrine and serotonin reuptake induces side effects similar to monoamine oxidase inhibitors, which can include serotonergic toxicity induced seizures.
- Tramadol is metabolized by the cytochrome P450 enzymes 2D6 and 3A4, and those patients with abnormal hepatic metabolism would be more likely to experience tramadol toxicity.
- Additionally, cytochrome P450 2D6 metabolism has been shown to be highly variable in patients less than 12 years old, including genetic 2D6 polymorphisms.
- Tramadol and its active metabolite are excreted into the breastmilk of nursing mothers.

Summary

- The warning announcement additionally emphasizes that tramadol and single-ingredient codeine are only approved for use in adult patients.
- The FDA recommends against the use of these medications in children less than 12 years old, specific patients less than 18 years old, and breastfeeding mothers of any age.
- To accompany the recommendation, the FDA added contraindications to the labeling of both tramadol and codeine products for use in patients less than 12 years of age.
- Also, tramadol received a contraindication for its use in patients under the age of 18 for postoperative pain management after an adenoidectomy and/or tonsillectomy.
- The same contraindication was applied to codeine in 2013.
- Warnings were added to the labeling of tramadol and codeine products to recommend against their use in patients between 12 and 18 years old with obesity or severe pulmonary conditions such as obstructive sleep apnea.
- The warnings about the risk of breastfeeding while taking these medications were emphasized due to the serious risks to breastfed infants including excessive sedation, and fatal respiratory depression.
- The FDA recommends that alternative analgesics should be used in place of tramadol and codeine for the treatment of pain in these patients.
- Also, they recommend that since cough is generally a symptom of other pathology, antitussive intervention may not be necessary, especially with codeine.

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