藥物不良反應工作小組藥物安全警訊通告 107.08

美國食品藥物管理署(FDA)用藥安全資訊風險溝通:

長期服用Azithromycin於預防經造血幹細胞治療後之閉塞性細支氣管炎可能增加復發之風險

摘要說明：

血液及淋巴相關癌症病患經造血幹細胞治療後與增加閉塞性細支氣管炎(bronchiolitis obliterans)有關，早先研究建議長期給予 Azithromycin 可預防閉塞性細支氣管炎的發生。

位於法國的 ALLOZITHRO 臨床試驗為第三期多中心隨機雙盲試驗，實驗組一週服用 Azithromycin 250mg 三次，持續兩年，與安慰劑組比較。此試驗於完成收納 480 名受試者後 13 個月，因發現實驗組有癌症復發及死亡率增加的情形而終止試驗。實驗組有 32.9% (n=77) 病患癌症復發，安慰劑組則為 20.8% (n=48)；試驗開始的前幾個月兩組間死亡率相似，然而隨後發生實驗組有 95 位病患死亡，兩年的生存率為 56.6%，安慰劑組有 66 位病患死亡，兩年的生存率為 70.1%。美國食品藥物管理署將再進行審核其他數據，並在審核完成後提出結論及建議。

目前無論是美國或台灣核准的適應症皆無用於預防經造血幹細胞治療後之閉塞性細支氣管炎發生。

醫療人員注意事項：

1) 不應長期服用 Azithromycin 於預防經造血幹細胞治療後之閉塞性細支氣管炎發生。

2) 正在服用 Azithromycin 為預防治療之病患不應在未經醫療人員評估的情況下自行停藥。

3) 醫療人員若懷疑病人因為使用藥品導致不良反應發生時，請立即線上通報藥物不良反應及登入於藥物過敏/不良反應記錄中。

院內品項：
Zithromax ®(Azithromycin) 250 mg/tab 日舒錠
Zithromax ®(Azithromycin) 40mg/mL，15mL/Bot 日舒懸液用粉劑

北醫藥物不良反應工作小組  敬啟
臨床藥學組 呂懷恩 藥師
（分機 8443/8444）
FDA warns about increased risk of cancer relapse with long-term use of azithromycin (Zithromax, Zmax) antibiotic after donor stem cell transplant

Safety Announcement

[8-3-2018] The U.S. Food and Drug Administration (FDA) is warning that the antibiotic azithromycin (Zithromax, Zmax) should not be given long-term to prevent a certain inflammatory lung condition in patients with cancers of the blood or lymph nodes who undergo a donor stem cell transplant. Results of a clinical trial found an increased rate of relapse in cancers affecting the blood and lymph nodes, including death, in these patients. We are reviewing additional data and will communicate our conclusions and recommendations when our review is complete.

The serious lung condition for which long-term azithromycin was being studied called bronchiolitis obliterans syndrome is caused by inflammation and scarring in the airways of the lungs, resulting in severe shortness of breath and dry cough. Cancer patients who undergo stem cell transplants from donors are at risk for bronchiolitis obliterans syndrome. The manufacturer of brand name azithromycin is providing a Dear Healthcare Provider letter on this safety issue to health care professionals who care for patients undergoing donor stem cell transplants.

Azithromycin is not approved for preventing bronchiolitis obliterans syndrome. It is an FDA-approved antibiotic used to treat many types of infections affecting the lungs, sinuses, skin, and other parts of the body. The drug has been used for more than 26 years. It is sold under the brand names Zithromax and Zmax and as generics by many different drug companies. It works by stopping the growth of bacteria that can cause infections.

There are no known effective antibiotic treatments for prophylaxis of bronchiolitis obliterans syndrome. Health care professionals should not prescribe long-term azithromycin for prophylaxis of bronchiolitis obliterans syndrome to patients who undergo donor stem cell transplants because of the increased potential for cancer relapse and death.

Patients who have had a stem cell transplant should not stop taking azithromycin without first consulting with your health care professional. Doing so could be harmful without
your health care professional’s direct supervision. Talk with them if you have any questions or concerns about taking this medicine.

Researchers in France identified this increased risk of cancer relapse and death while conducting a clinical trial investigating the effectiveness of long-term azithromycin to prevent bronchiolitis obliterans syndrome in patients who undergo donor, or allogenic, stem cell transplants for cancers of the blood and lymph nodes. The researchers concluded that the risks of long-term azithromycin exposure after donor stem cell transplantation may exceed the benefits. The trial could not determine why the rates of cancer relapse and death were higher with azithromycin.

The researchers stopped the ALLOZITHRO\(^1\) trial approximately 13 months after the study completed enrollment of 480 patients because an unexpected increase in the rate of both cancer relapses and death was observed in patients taking azithromycin. Cancer relapse was observed in 77 patients (32.9\%) with azithromycin treatment compared to 48 patients (20.8\%) with placebo, which is an inactive treatment. A total of 95 patients died in the azithromycin treatment group versus 66 patients in the placebo group; thus, the 2-year survival rate was 56.6\% in azithromycin-treated patients compared to 70.1\% in those receiving a placebo. In the first few months of the trial, the death rate was about equal between those receiving azithromycin and placebo. However, an imbalance occurred subsequently and continued until the 2-year time point when the study was stopped.

To help FDA track safety issues with medicines, we urge health care professionals and patients to report side effects involving azithromycin and other drugs to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Reference


Related Information

Azithromycin (marketed as Zithromax or Zmax) Information

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines
Efficacy of Azithromycin to Prevent Bronchiolitis Obliterans Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation (ALLOZITHRO)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Sponsor:
Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):
Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier: NCT01959100

Recruitment Status: Active, not recruiting
First Posted: October 9, 2013
Last Update Posted: July 23, 2018

First Submitted Date: October 7, 2013
First Posted Date: October 9, 2013
Last Update Posted Date: July 23, 2018
Study Start Date: February 2014
Actual Primary Completion Date: April 2017 (Final data collection date for primary outcome measure)

Current Primary Outcome Measures (submitted: September 1, 2015)
Airflow decline (AFD)-free survival [Time Frame: 2 year after allogeneic HSCT]
Defined on the criteria from Chien JW et al (Am J Resp Crit Care Med 2003;168:208-14) by an annualized decline of percent predicted forced expiratory volume in 1 second (FEV1) of more than 5%

Original Primary Outcome Measures (submitted: October 8, 2013)
Airflow obstruction (AFO)-free survival [Time Frame: 2 year after allogeneic HSCT]

Change History
Complete list of historical versions of study NCT01959100 on ClinicalTrials.gov Archive Site

Current Secondary Outcome Measures (submitted: December 23, 2016)
- Overall survival [Time Frame: within 2 years of inclusion]
- Occurrence of late-onset pulmonary non-infectious complications (=bronchiolitis obliterans syndrome, SBO) [Time Frame: within 2 years after inclusion]
bronchiolitis obliterans syndrome (SBO) is defined as the absence of infection with an forced expiratory volume in 1 second (FEV1) of <75% of predicted or a decline of > 10% and FEV1/Slow vital capacity (SVC) < 0.7 or residual volume (RV) or RV/total lung capacity (TLC) > 120%, and interstitial lung disease, which is defined as the onset of new interstitial lung abnormalities observed with a lung CT scan and the absence of infection.

- Variation of pulmonary function testing parameters [Time Frame: within 2 years after inclusion]
  
  variation in mean forced expiratory volume in 1 second (FEV1) decline, forced vital capacity (FVC), residual volume (RV), Total Lung capacity (TLC), Forced expiratory flow at 25% point to the 75% point of Forced Vital Capacity (FEF25-75%) as compared to baseline values (at inclusion)

- Occurrence of acute and chronic extra-thoracic graft versus host disease (GVHD) [Time Frame: within 2 years after inclusion]

- Cumulative incidence of hematological relapse [Time Frame: within the 2 years after inclusion]

- Quality of life [Time Frame: within 2 years after inclusion]

- Tolerance [Time Frame: within 2 years of inclusion]
  
  adverse events

- Cumulative dose of steroids treatment [Time Frame: within the 2 years after inclusion]

<table>
<thead>
<tr>
<th>Original Secondary Outcome Measures</th>
<th>ICMJE (submitted: October 8, 2013)</th>
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<tbody>
<tr>
<td>Overall survival [Time Frame: within 2 years of inclusion]</td>
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<td>Occurrence of late-onset pulmonary non-infectious complications (=bronchiolitis obliterans syndrome, SBO) [Time Frame: within 2 years after inclusion]</td>
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- Variation of pulmonary function testing parameters [Time Frame: within 2 years after inclusion]
  
  variation in forced vital capacity (FVC), residual volume (RV), Forced expiratory flow at 25% point to the 75% point of Forced Vital Capacity (FEF25-75%) as compared to baseline values (at inclusion)

- Occurrence of acute and chronic extra-thoracic graft versus host disease (GVHD) [Time Frame: within 2 years after inclusion]

- Quality of life [Time Frame: within 2 years after inclusion]

- Tolerance [Time Frame: within 2 years of inclusion]
  
  adverse events

- Cumulative dose of steroids treatment [Time Frame: within the 2 years after inclusion]

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<th>Original Other Outcome Measures</th>
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**Descriptive Information**

<table>
<thead>
<tr>
<th>Brief Title</th>
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<tbody>
<tr>
<td>Efficacy of Azithromycin to Prevent Bronchiolitis Obliterans Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation - Ta...</td>
<td>ICMJE</td>
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<tr>
<td><strong>Official Title</strong></td>
<td>Evaluation of the Efficacy of Azithromycin to Prevent Bronchiolitis Obliterans Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation</td>
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<td>-------------------</td>
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<tr>
<td><strong>Brief Summary</strong></td>
<td>The occurrence of bronchiolitis obliterans syndrome (SBO) after allogeneic hematopoietic stem cell transplantation (HSCT) is considered to be a chronic pulmonary graft versus host disease (GVHD) that is associated with significant mortality and morbidity. The reported incidence of SBO varies from 6 to 26% of allogeneic HSC recipients and is usually diagnosed within 2 years after transplantation. The diagnosis of SBO relies on the occurrence of a new airflow obstruction identified during pulmonary function testing, and the definition differs between studies. Currently, no curative immunosuppressive treatment is available, and recent data suggest that the use of these treatments, especially corticosteroids, should be limited because of their toxicity. The impairment of lung function parameters is likely caused by fibrous small airway lesions. Few data on the pathogenesis of SBO after allogeneic HSCT are available. Several hypotheses are based on the occurrence of SBO during chronic graft rejection after lung transplantation, which shares many clinical and histopathological similarities with SBO after allogeneic HSCT. One hypothesis is that the first step leading to SBO is lung epithelium injury. SBO is then identified as an alloimmune reaction with only one clearly identified risk factor: extrathoracic chronic GVHD. Due to their anti-inflammatory and immunomodulatory properties, recent data suggest that low-dose macrolides may be effective at preventing SBO after lung transplants. This well-tolerated treatment may be useful for preventing SBO after allogeneic HSCT. The objective of this Phase 3 multicentre randomized, double-blinded, clinical trial is to evaluate the efficacy of azithromycin in preventing BO syndrome after allogeneic HSCT in patients with malignant hematological diseases.</td>
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<tr>
<td><strong>Detailed Description</strong></td>
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<tr>
<td><strong>Study Type</strong></td>
<td>Interventional</td>
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<td><strong>Study Phase</strong></td>
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</table>
| **Study Design** | Allocation: Randomized  
Intervention Model: Parallel Assignment  
Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)  
Primary Purpose: Prevention |
| **Condition** | Malignant Hematological Diseases |
| **Intervention** | • Drug: Azithromycin  
250 mg x 3/week per os during a meal for a period of 2 years  
• Drug: Placebo  
250 mg x 3/week during a meal for a period of 2 years |
| **Study Arms** | • Experimental: Azithromycin  
250 mg x 3/week during a meal for a period of 2 years  
Intervention: Drug: Azithromycin  
• Placebo Comparator: Placebo  
250 mg x 3/week during a meal for a period of 2 years.  
Intervention: Drug: Placebo |

* Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.

**Recruitment Information**

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<tr>
<td>Actual Enrollment ICMJE (submitted: May 20, 2016)</td>
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<td>Original Estimated Enrollment ICMJE (submitted: October 8, 2013)</td>
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<td>Estimated Study Completion Date</td>
<td>August 2020</td>
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<td>Actual Primary Completion Date</td>
<td>April 2017 (Final data collection date for primary outcome measure)</td>
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**Eligibility Criteria ICMJE**

Inclusion Criteria:
- Patients > 16 years old
- Experimenting an allogeneic HSCT for a hematologic malignancy
- Pre-transplantation Pulmonary Function Testing
- With written informed consent

Exclusion Criteria:
- Allergy or Intolerance to azithromycin, macrolides or ketolide or excipient
- Prolonged corrected QT (QTc) interval (>450 msec)
- Taking medications that prolong the QTc interval (Cisapride, ergotamine, dyhydroergotamine)
- Taking ergotamine and dyhydroergotamine due to the risk of ergotism
- Family history of a prolonged QTc interval.
- History of congestive heart failure
- Taking colchicine Severe liver insufficiency • History of infection due to atypical mycobacteria

**Sex/Gender**
- Sexes Eligible for Study: All

**Ages**
- 16 Years and older (Child, Adult, Older Adult)

**Accepts Healthy Volunteers**
- No

**Contacts ICMJE**
- Contact information is only displayed when the study is recruiting subjects

**Listed Location Countries ICMJE**
- France

**Removed Location Countries**
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<td><strong>Has Data Monitoring Committee</strong></td>
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<td><strong>U.S. FDA-regulated Product</strong></td>
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<td><strong>Verification Date</strong></td>
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Data element required by the [International Committee of Medical Journal Editors](https://www.icmje.org) and the [World Health Organization ICTR](https://www.who.int/ictrp)
阿奇霉素

Azithromycin

阿奇霉素是一种窄效抗菌药物，主要用于治疗支气管炎和肺炎。其作用机制是抑制细菌的50S亚基，从而阻止细菌的蛋白质合成。阿奇霉素对多种革兰氏阳性菌和革兰氏阴性菌具有显著的抗菌活性，尤其是对肺炎链球菌、流感嗜血杆菌和肺炎支原体等具有高度的抗菌活性。阿奇霉素对革兰氏阴性菌的活性也较强，如对大肠杆菌、克雷伯杆菌和铜绿假单胞菌等具有较好的抗菌效果。阿奇霉素的抗菌谱较广，对多种支原体和衣原体也具有显著的抗菌活性。阿奇霉素对某些耐药菌株也具有一定的抗菌活性，如对部分耐甲氧西林金黄色葡萄球菌（methicillin-resistant Staphylococcus aureus, MRSA）具有一定的抗菌活性。阿奇霉素在体内吸收迅速，起效快，疗效持久，对肺部感染和呼吸道感染的治疗效果显著。阿奇霉素在老年人和儿童中的应用已广泛推广。
Blood potassium, and 15 mg of patients; the effect of the drug on the serum
of patients cannot be excluded. A meta-analysis of the data, however, showed
significant effects on blood potassium levels.

The drug may induce hypokalemia, and this may be
especially problematic in patients with renal insufficiency. It is,
therefore, important to monitor serum potassium levels closely
in such patients.

Trimethoprim/sulfamethoxazole,

Sildenafil,

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Efavirenz,

Coumarin,

Atorvastatin,

Methylenediamine

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