e-LEARNING OBJECTIVES: to know the adverse drug reactions of the antitubercular drugs, and how to fill a yellow card.

Clinical case

A 55 years old man, with coxarthrosis, in chronic therapy with paracetamol and diclofenac, goes to the doctor with complaints about dyspnoea, hematic cough which he has experienced during the past month. After some radiologic and blood examination a diagnosis of tuberculosis is made.

The patient starts treatment with isoniazide, rifampin, ethambutol and pyrazinamide for six months with blood exams every month. After seven days of treatment he complained of nausea, anorexia and abdominal pain.
The physician advised the patient to take the drugs with small meals and with a small sip of water.
Comment: The first thing to do is to try to maintain the anti-Tb therapy. Only if the symptoms remain, the therapy will be stopped.

Thanks to the advices of the physician the patient feels better, but after other two weeks he comes back to the hospital complaining red urine. He had noted this sign one month ago, but he did not give importance to that; now he is scared for his therapy anti-TB and he asks for medical advice.

The hospital doctor reassured him, and he advised the patient not to be scared and to continue his therapy. The red/orange color of the urine is an effect of rifampin, without any negative effect. The patient continued his anti-TB therapy.

After another week the patient came to the hospital: he was pale, with fever chills, and malaise. The blood exams showed anemia (HB 8.7g/dl, WC 21,000 per microl), LDH 4814 U/l, serum creatinine 4,14 mg/dl, hemoglobinuria (blood in the urine) ++++.

A Direct Coombs test was positive confirming the diagnosis of hemolitic anemia and consequent renal failure (tubular necrosis).
Rifampin and isonazide were stopped, and a week after anemia was less severe and the level of creatinine fell to 2,2 mg/dl.

The patient continued the antitubercular therapy with the other drugs.

At this point fill the yellow card with the data of the adverse event.

E-LEARNING OBJECTIVES

The clinical case presented herein wants to provide an example of how to manage reporting of suspected ADRs of anti-TB drugs.
The exercise is designed to improve the participant's practical knowledge on the reporting of suspected ADRs. After completing the assignment, the participant should be able to properly recognize some of the most severe anti-TB ADR symptoms and to correctly identify the main elements that are to be present in an ADR report.

Clinical case n. 3 – A 29-year-old man very tired

A 29-year-old man comes to see the doctor with lower back pain which he has had for two months, persistent cough which has been treated with amoxicillin without results, fever, night sweats, chills and hemoptysis. He smokes 20 sigarettes a day, he drinks a beer a day, he did not have any other illness in his life.
He also reports that has lost about 15 kg of weight and that he always feels very tired.
On the basis of chest X-Ray and GeneXpert, he is diagnosed with pulmonary TB, and treatment is started with isoniazid, rifampin, ethambutol and pyrazinamide. The patient decides to stop smoking.

After a few weeks the patient, who started eating again and felt better, complained of multiple joint pain, marked anorexia and yellow sclera.

In this case you suspect that:

1. the therapy didn't work
2. the patient has a drug-induced arthritis
3. the patient didn't take the therapy
4. **the patient may have a drug-induced hepatitis**

Comment: Polyarthralgia and anorexia are prodromal signs of hepatitis. Scleral jaundice indicates a liver disease.

Blood tests give these results:
AST = 317 U/L
ALT = 583 U/L
AP 1416 U/L
Total bilirubin 60 micromol/L
Even if there is not a specific test for drug induced hepatitis, as ALT are more than 5 times the normal values and bilirubin is >40 micromol/L, it is likely to suppose a drug induced hepatitis. All four drugs used are hepatotoxic, but ethambutol is less toxic than the others.

The doctors decide to whithdraw all therapy.

After how long will the doctors be able to start the treatment again?

1. after the normalisation of laboratory tests
2. **after the normalisation of symptoms and laboratory tests**
3. after the symptoms have disappeared, regardless of the laboratory tests
4. two months after the normalization of laboratory tests

Comment: When it is not possible to follow the patient by monitoring the laboratory tests, it is necessary to wait at least two weeks after the disappearance of the jaundice before starting the antitubercular therapy again.

When the antitubercular treatment will be started again, what should be done?

1. use other drugs than those already used
2. start the drugs one at a time
3. **start the drugs one at a time, beginning with rifampin**
4. use all drugs immediately to avoid resistance

Comment: The reason for starting with rifampin is because of the lower frequency of hepatotoxicity compared to isoniazid and pyrazinamide, and the greater efficacy. Isoniazid can be reintroduced after 3 to 7 days. Patients who have developed hepatitis but tolerate rifampin and isoniazid should not add pyrazinamide.

Minister of Health of Tanzania, Manual for the Management of Tuberculosis and Leprosy, Sixth Edition, 2013, page 44(https://ntlp.go.tz/site/assets/files/1047/ntlp_manual_sixth_edition_2013.pdf)