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RESEARCH ARTICLE

BIOTHERAPY DURING CHRONIC INFLAMMATORY BOWEL DISEASE: AN OVER-RISK OF TUBERCULOSIS REACTIVATION?

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Abstract

Anti-TNFα have revolutionized the management of chronic inflammatory rheumatic and intestinal diseases; however, they are at high risk of reactivation of latent tuberculosis. These are most often extra-pulmonary tuberculosis and disseminated forms which occur during the first year and which can be avoided by screening and prophylactic treatment. The aim of this publication is to describe the epidemiological, clinical, biological, radiological and evolving data of patients having triggered tuberculosis under anti TNFα treatment followed at the Hassan II hospital center (CHU) in Fez during the period between January 2012 and January 2021. During this period, we collected 130 patients under anti TNF alpha of which 84.5% of patients are on Infliximab; 15.5% on Adalimumab. Active tuberculosis occurred in 4.6% of patients whose mean age is 35.5 years and the sex ration is 5H / 1F. The duration of onset is on average after 5 sessions of anti TNF alpha. A phtysio assessment was carried out in all our patients before starting the anti TNF α, 2 of which were IDR positive; completed by quantifying it which came back positive in a single patient.

Introduction:-

The contribution of TNF (Tumor Necrosis Factor) cytokine inhibitors is a major advance in the management of multiple chronic inflammatory bowel, rheumatic and skin diseases. [1]

TNF is one of the central cytokines in the process of protection against infections. It was therefore predictable that its inhibition could be associated with an increased risk of infections in general, and in particular the reactivation of latent tuberculosis (LTB) which is a considerable challenge. [1].

These reactivated tuberculoses had unusual features; They had a rapid onset time (3 months after the start of treatment) and an unusual frequency of disseminated and severe forms. [2]

The severity and frequency of these reactions imposed recommendations and precautions for use with the introduction of systematic screening and prevention procedures. [2].

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The aim of this article is to evaluate the tools for diagnosing latent tuberculosis infection (LTBI) in patients who are candidates for anti-TNF-α therapy in order to treat it and prevent its reactivation under anti TNF alpha therapy.

Materials &Methods:-

We conducted a retrospective, descriptive study of patients followed for chronic inflammatory bowel disease under anti TNF alpha (infliximab /adalimumab) and who developed tuberculosis whose diagnosis is retained on a bundle of clinical, biological and radiological arguments within the hepato-gastroenterology department at the CHU HASSAN II of Fez. This study was carried out over a period spread between January 2012 and January 2021 with a total duration of nine years. We have thus identified 6 cases of tuberculosis declared under anti TNFα.

Clinical Case N°1:

This is a 63 year old patient; followed for 10 years for UC in pancolitis put initially on 6-mercatopurines with a good clinical, biological and endoscopic evolution. The patient was admitted in 2019 for PEC of severe acute colitis with endoscopic signs of severity put on truelove regimen with partial response hence the indication of anti TNFα treatment in combotherapy. A phthisical assessment was performed, showing a negative TST; 3 negative BK sputum; normal chest x-ray; he was given the loading dose and 4 maintenance doses every 8 weeks, i.e. 7 doses of infliximab in total. The evolution was marked by the patient's improvement on the digestive level. However, examination of the lymph nodes revealed a painless, fixed, right lateral cervical ADP measuring 1.5 cm with feverish peaks. However, the examination of the lymph nodes showed a fixed painless right latero-cervical ADP of 1.5 cm with feverish peaks of 39; a biological and radiological check-up was done: CRP negative; LDH and Beta 2 microglobulins correct; a cervical ultrasound with CTAP scan was done showing multiple right latero-cervical, Jugulo carotid and spinal ADPs; then he underwent a cervicotomy with excisional biopsy whose histological examination came back to show a tuberculous adenitis. The aftermath of the cervicotomy was marked by fistulization of the skin with non-healing of the wound and superinfection. He was put on anti-bacillary treatment for 9 months with local care. On the luminal level the patient was in clinical remission with a fecal calprotectin at 70 µg/g hence the decision to put the patient on mesalasin 2g/dr given the refusal of anti tnf by the patient and the clinical and endoscopic and biological remission.In March 2021 he presented a mild relapse with rectal syndrome and weight loss with night sweats. A rectosigmoidoscopy was performed: objectifying an erythematous and ulcerative left UC. Imaging showed an increase of the inflammatory digestive parietal thickening of the whole colonic framework with some mesenteric lymph node formations and at the level of the IDF, of oval shape, necrotic for some of them, and with a small sub-centimeter axis. The decision was to resume the combotherapy after agreement of the pneumologists. At present, the patient tested covid positive and has not yet started his anti TNF alpha treatment.

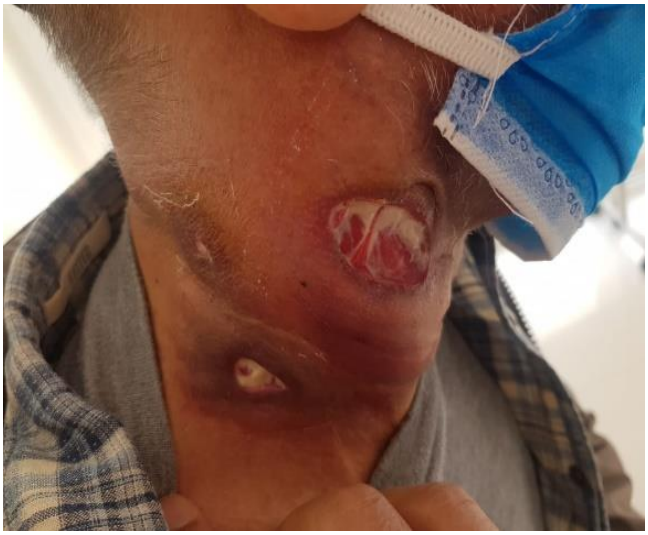

Figure 1:- Unhealed cervicotomy wound with fistulization to the skin.

Clinical Case N°2:

A 34 year old patient, chronic smoker for 14 years, followed in our training program for the treatment of ileal stenosing crohn's disease for 7 years, put on Azathioprine, the evolution of which was marked by the onset of an occlusive syndrome. An abdominal CT scan was performed, which revealed a small bowel obstruction on an

inflammatory thickening of the IAD. The patient was taken to the operating room and the exploration showed an enormous distension of the bowel upstream of a fibrous thickening of the IAD; an ileo-caecal resection was performed taking away the fibrous zone and the fistula (about 70 cm of small intestine) with the creation of a double stoma at the BW in the right iliac fossa. The patient was then put on Azathioprine 150mg/day after a negative phthisis workup with 3 sputum samples, IDR and chest x-ray. Continuity was re-established 2 months later; the post-surgery endoscopic control showed a rutgeerts score i2. The decision of the IBD staff was to put the patient on Adalimumab; after 5 doses of anti TNF alpha the evolution was marked by the installation of asthenia, myalgias and fever associated with a cough with sputum streaked with blood motivating his consultation; a thorax X-ray was made objectifying a tubercular miliary put on anti bacillary treatment for 9 months with good clinical evolution; currently stable patient on the digestive plan; has not yet resumed the background treatment.

Clinical Case N°3:

A 34-year-old patient with a history of anal fistula. Followed in our training program for treatment of ileocoecal stenosing and fistulizing crohn's disease, initially put on Azathioprine after a pre-immunosuppressive workup showing a 12 mm TST, supplemented by a positive quantiferon. The follow-up was marked by repeated urinary tract infections with fecal colic. The entero MRI was done to objectify a collection of the psoas making 4 cm*2 cm with individualization of an entero vesical fistula with thickening of the vesical wall and dilatation ureteropyelocaliciale right completed by a cystoscopy which individualized a fistula of the bottom bladder lateralized on the right. The IBD staff decided to operate on the patient; he underwent an ileo-caecal resection with removal of the pathological loop. After 4 sessions of Infliximab, the patient presented a respiratory symptomatology made of dry cough evolving in a context of feverish sensation with a left liquid effusion syndrome on clinical examination. A chest X-ray was taken, showing a left pleurisy of moderate size. The pleural puncture revealed an exudative fluid with a predominance of lymphocytes and the pleural biopsy showed granulomatous pleuritis without caseous necrosis. The therapeutic decision was to put the patient on anti-bacillary drugs for 9 months with cessation of anti TNF alpha. The clinical evolution was marked by the drying up of the pleurisy; and on the digestive level, the patient had just resumed his anti TNF alpha treatment.

Clinical Case N°4:

Patient aged 23 years. Followed in our training for UC disease an pancolitis since the month 11/2016 .Put initially on corticosteroids with rectal enema and mesalazine 3g/dr .Then the patient presented a push where the decision to put the patient on azathioprine without clear improvement to start and therefore put on a combotherapy based on adalimumab complicating a medullary aplasia regulated after the cessation of immunosuppressive treatment and put on NOPOGEN . Patient hospitalized afterwards for management of severe acute colitis with signs of endoscopic severity without response to truelove and anti TNF alpha regimens " 2 doses of infliximab " and therefore she benefited from a subtotal colectomy with a right ileostomy and a left colostomy. A phthisis check-up was requested at the time of the acute severe colitis, showing: a positive TST at 22 mm with a left apical pulmonary focus on the chest X-ray; 3 BKs not done (the patient did not spit) with a positive gastric tube. A pulmonary TB was retained, the patient was put on antibacillary treatment for 6 months, declared to be discharged under no background treatment for her UC disease due to the immunodepression. On the digestive plan: the patient reported the emission of mucus by the sigmoidostomy and by the anus. An endoscopy was made objectifying the presence of an erythematous and congestive mucous membrane from the AM, seat of superficial ulcerations by place with the presence at 18 cm of a regular impassable narrowing, that is to say a Mayo score at 3. The decision was to resume infliximab except that the patient presented a severe allergic reaction at S2, hence the definitive discontinuation of infliximab. Currently, the patient is a candidate for Ustekinumab-based treatment after the appearance of multiple anal fistulas with pus discharge that was stopped after placement of the fistula and the use of antibiotics.

Clinical Case N°5:

Patient age 32 years followed for left UC since 2018 put initially under cortico 40 mg and mesalazine enema with improvement of the number of stools but seen the cortico dependence; an immunosuppressive treatment was indicated. He benefited from a phtysio assessment made of 3BK sputum coming back negative with a positive IDR at 14 mm and positive quantiferon. A pneumo opinion was requested indicating the realization of a bronchial endoscopy coming back normal, direct examination with culture in search of negative BAAR completed by a thoracic canner objectifying some pulmonary micronodules which could be infectious. As a result, the patient was put on azathioprine since there was no contraindication. The patient was then admitted for treatment of a severe relapse, with an endoscopic and radiological check-up showing UC in the form of pancolitis and relapse. The decision was to put the patient on anti TNF based on infliximab, but in view of the tuberculinic change of heart, the

presence of micronodules on the CT scan, and the weight loss, the patient was put on antibacillary chemoprophylaxis for 1 month before starting anti TNF alpha. After three sessions of infliximab, the patient developed lymph node tuberculosis and was put on anti-bacillary treatment for nine months. The patient is five months into his anti-bacillary treatment and has not yet started the basic treatment for his UC disease.

Clinical Case N°6:

Patient aged 44 years. Followed since 2003 for UC put on corticosteroid therapy.admitted in 2013 for severe acute colitis put on truelove regimen with good clinical and biological evolution then put on azathioprine 100mg /dr.the endoscopic control objectified a UC in pancolitis in remission; fecal Calprotectin:838. The decision was to do the dosage of metabolites: 6TGN coming back high at 1002 and 6MMP low at 1539, so we conclude to a resistance to Azathioprine so we decide to put the patient on Infliximab-based combotherapy. After 6 sessions of Infliximab, the patient presented with a painful scrotal swelling, with ultrasound examination showing a thickened and infiltrated appearance of the scrotal soft tissues with visualization of a collection of about 2.7 cm, a right intra-testicular tissue nodule of about 40 mm of suspicious appearance, and a flattening of the abscess. Histological examination showed epididymal tuberculosis. The patient was put on anti-bacillary treatment for 9 months with a good clinical and radiological response.On the digestive level, the patient remained stable with 3 non glairo bloody stools with minimal rectal sundrome. The colonoscopy of control objectified a stenosis to 2cm of the impassable irregular AM; biopsy made with with the anatomopathological examination: aspect of fleshy bud without dysplasia nor sign of malignancy. The calprotectin dosage made coming back high at 1000. The enteroscanner was done objectifying a distal rectal parietal thickening extended on 4.5 cm with centered stenosis.patient is programmed for a colonoscopy with dilatation then to a treatment based on anti TNF.

Clinical DATA	Results
Age	35 years [23-61 years]
Sex ratio	5M/1F
IBD type UC Crohn	04 patients 02 patients
Anti TNF alpha type Infliximab Adalimumab	 05 patients 01 patient
Average number of sessions before TB	05 séances

Tuberculosis type	
Lymph node	2 patients
Pleural	1 patient
Testicular	1 patient
Pulmonary	1 patient
Miliary	1 patient

Table 1: Clinical Information of patients.

Discussion:

Tuberculosis is a contagious airborne disease that primarily affects young people in developing countries with low socioeconomic status. It presents a major health problem in low- and middle-income countries. [3]

Two billion people worldwide have latent tuberculosis (LTBI) [4].

The overall lifetime progression of latent TB to overt disease is approximately 5-10%. However, there are patients who have a higher risk of reactivation "4 to 5 times more", especially immunocompromised patients, especially those with AIDS or on anti-TNF-α drugs. [5-6-7-8]

Tuberculosis secondary to immunosuppressive therapy could be prevented by diagnosis and treatment of latent tuberculosis infection (LTBI).

If active TB occurs shortly after starting anti-TNF-α, this could represent reactivation of LTBI, whereas late presentation of disease may be due to either delayed reactivation or recently acquired infection. [9]

Incidence of tuberculosis with anti-TNF:
The 2001 study by Kaene et al. in the United States reported 70 cases of TB on anti-TNFα drugs between 1998 and 2001. [10]

A retrospective Algerian study of 7 centers including IBD patients on anti-TNFα therapy between November 2010 and July 2014 reported an incidence of 1.8% or 4 patients, 2 of whom had previously received prophylactic antituberculosis treatment for LTBI and 2 had no TBL and developed TB after one year of treatment. [11]

Another French study investigated the risk of TBA under anti TNF during psoriasis treatment in Eight centers; they reported a total of 12 patients between 2006 and 2014. [12]

According to a report from Denmark, approximately 6,000 patients have received anti-TNF-α therapy in that country over the past 10 years. With 15 reported cases of TB, this rate corresponds to an incidence of 25 per 105 per year. [13]

A Swedish study in 2008 reported a nearly 4-fold increase in risk, with 13 cases of TB in patients treated with anti-TNF-α. [13]

Subjects at risk of tuberculosis reactivation on anti TNF alpha : [2-14]
1. Subjects with untreated primary infection.
2. Subjects who had TB in the past or who have radiological sequelae without certainty of correct treatment (treated before 1970 or who have not had at least 6 months of treatment including at least 2 months of rifampin + pyrazinamide).
3. Subjects who have had close contact with a patient who has developed pulmonary TB.
4. Subjects with a tuberculin TST > 5 mm distant from BCG (> 10 years) or phlyctenular, never having had active TB and never having received treatment.
5. Subjects from highly endemic areas (subject to special vigilance).
6. health care facility staff, prisoners and prison staff
7. homeless persons, drug users, and persons working with migrants.

Pre-therapeutic assessment:
The recommendations of the French Agency for the Safety of Health Products (Afssaps) of 2002 and revised in 2005 propose : [15]

A detailed interrogation to look for :
1. BCG vaccination.
2. The results of previous tuberculin TSTs.
3. The notion of contagion (family history, including in childhood).
4. The notion of exposure (origin or prolonged stays in highly endemic countries).
5. Personal and family history of TB or anti-tuberculosis treatment (drugs, dose and duration).

Physical examination for signs of TB disease: general signs, pulmonary and extra pulmonary signs.

Chest X-ray: in case of images suggestive of TB sequelae, a pneumological opinion with discussion of a complementary thoracic scanner, sometimes bronchial fibroscopy.

An intradermal tuberculin test (IDR): [16-17-18]
0.1 ml of tuberculin or 5 units of liquid tuberculin with reading of the induration area in millimeters between the 48th and 72nd hour.

An induration below 5 mm is considered negative; an induration of 10 and 15 mm is the minimum size accepted to consider the test positive.

Immunocompromised patients, including those treated with anti-TNF-α, are classified as high-risk patients, for whom an induration of at least 5 mm on the IDR is presumed to be a positive result.

If phlyctenular TST: sputum or tube test for BK 3 days in a row.

The possibility of false-positive TSTs in cases of BCG vaccination less than 10 years and other NTMs (nontuberculous mycobacteria) makes interpretation of results more difficult because of the decreased specificity of the test. [19]

False negatives are frequent in cases of immunosuppression, so some people need to use a second test (after 7-10 days, double dose) to obtain a booster effect (amplification of the response). This method is recommended in Spain; it would save 8-14% of TBL diagnosis. [20]

The lack of specificity of the TST has led to the development of interferon γ release assays (IGRA), of which there are two types: Quantiferon-TB Gold IT and T-Spot.TB .

Their better sensitivity in immunocompromised subjects and higher specificity than TST due to lack of cross-reactivity with BCG or DTM make these two tests more effective. [21-22]

However, they cannot differentiate between active TB and LTBI. [25]

On the other hand, a blood test performed after an TST may be falsely amplified by the injected tuberculin (booster effect); and some authors recommend not performing blood tests from the 3rd day and until the 3rd month after an TST. [24]

The approach to TBL screening:
The screening approach differs from one country to another; It is either to replace the TST by the IGRA (Germany, Sweden...), or to use the TST or the IGRA in the same way (United States, France...) or to perform the TST first, and then complete with the IGRA if the TST is doubtful (Canada, Spain...)[25]

It should also be noted that the European Society of Respiratory Diseases suggests not to perform the TST in case of BCG vaccination but rather the IGRA [26].

The ECCO (European Crohn's and Colitis Organisation) consensus of 2009 recommends in addition, to complete the TST with an IGRA test and mentions that the interest of a second TST (1-8 wk) can be considered in case of immunosuppression. [27]

The SAFEBIO expert panel prefers to use IGRA instead of TST in cases with a history of BCG vaccination because of the possibility of false-positive TST results in these patients. [28]

The UK National Institute for Health guidelines do not accept the TST alone to detect TBL in immunocompromised patients. Both should be performed at the same time or one after the other if the first test is negative. [29]

Prophylaxis for those at risk:
All patients receiving anti-TNF-α drugs with evidence of TBL should receive preventive therapy.Adherence to therapy is crucial in view of the fact that prophylaxis may be ineffective in approximately one-third of cases [30].

Some guidelines recommend deferring anti-TNF-α therapy until after completion of TB treatment. However, most authorities do not accept such a recommendation and suggest starting biological agents at least 1 month after initiation of anti-TB drugs[31-32].

Afssaps in 2005[15], had proposed 3 prophylaxis regimens for subjects at risk of TBL:

- Isoniazid alone (5 mg/kg/d), for 9 months in case of liver toxicity or elderly or cirrhotic subjects; this regimen seems to be the best validated because it allows to decrease by 60 to 90% the transition from LTBI to TB disease, with a low hepatotoxicity
- Isoniazid (4 mg/kg/day) + rifampicin (10 mg/kg/day), for 3 months; this regimen appears to be less well validated than isoniazid monotherapy; efficacy appears to be similar to isoniazid but is subject to the side effects of rifampicin
- Rifampicin (10 mg/kg/day) + pyrazinamide (20 mg/kg/day) in one dose for 2 months, in case of contraindication to isoniazid or isoniazid-resistant strains.

Finally, the possibility of active TB despite treatment of latent TB infection in patients treated with anti-TNF-α is still a concern. It is not known whether the occurrence of active TB in this situation is a newly acquired infection or a reactivation of a latent infection. [33]

- Yoshikawa et al. reported three cases of active TB in patients receiving anti-TNF-α despite treatment for LTI. [34]
- A study of 525 Korean patients with inflammatory bowel disease (365 anti-TNF-α naive and 160 on anti-TNF-α) reported a significantly higher incidence of TB in patients receiving anti-TNF-α compared with the naive case. LTBI was diagnosed in 17 patients (10.6%), They concluded that newly acquired pulmonary TB was more common than LTBI reactivation.[35]

Treatment of reactivated tuberculosis with anti-TNF alpha [20]:

Once the diagnosis of active TB is retained, discontinuation of anti-TNFα is warranted, and reporting to pharmacovigilance is recommended. The total duration of antibacillary treatment is depending on the affected organs, ranging from 6 to 18 months. It consists of a quadritherapy: Rifampicin (10 mg/kg/day), Isoniazid (4 mg/kg/day), Pyrazinamide (20 mg/kg/day) and Ethambutol (15 to 20 mg/kg) in a single dose for the first two months. This treatment is followed by dual therapy: Rifampicin + Isoniazid for 4 to 10 months depending on the location.

When should anti-TNF therapy be resumed after reactivation of tuberculosis?

If the interest of anti-TNF is considered major, anti-TNF treatment can be resumed after a minimum delay of antibacillary treatment greater than or equal to three months, after being reassured of the complete normalization of clinical, biological and radiological signs, and it is always necessary to evaluate the benefit/risk ratio before starting an anti-TNFα.

Conclusion:-

Given the risk of active TB in patients receiving anti-TNF-α therapy, preventive therapy for patients with LTBI should be initiated at least one month before the initiation of biologic agents. However, there is no "gold standard" for diagnosing LTBI. Given the low sensitivity and specificity of TST; whether IGRAs such as QFT-G should be accompanied by TST or even replace it is a matter of debate, and requires further studies to be able to recommend such a policy in low- and middle-income countries.

Conflicts of Interest

No conflict of interest for authors.

Authors Contributions

Collecting DATA and drafting article: HakimaAbid &Sarra Bahja;

Revising the manuscript: Ibrahimi SidiAdil, Mohammed El Abkari

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