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Anti-Tnf Side Effects in the Treatment of Chronic Inflammatory Bowel Disease

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ABSTRACT

IBD is a common, serious and disabling chronic digestive disease, Their different manifestations, whether digestive and extra-digestive, require a multi-professional care adapted to each specific patient. Anti-TNFs are now an essential therapeutic weapon in the management of inflammatory bowel disease (IBD). Their effectiveness in both the short and long term has been demonstrated in various studies. However short and long term anti-tnf results vary from patient to patient which can be explained in many cases by the significant number of discontinued treatment in patients that experience side effects. The purpose of our work is to study the different side effects occurring in patients under biotherapy, the management of these side effects and their prevention. We prospectively analyzed since four years the medical records of 54 IBD patients who received anti-TNF treatment. An exhaustive pre-therapeutic assessment was performed systematically in all patients. A clinical and biological control was carried out systematically before each therapeutic administration to search for undesirable reactions. Side effects were classified into several categories including immediate hypersensitivity reactions, dermatological complications, infectious, neurological, haematological, neoplasic and cardiac complications.

During this period, 54 patients were treated with biotherapies, representing 24.2% of all IBD patients. We observed 29 side effects, an incidence of 46% including two severe effects 3.5%, occurring on average after one month of treatment. The hematological undesirable effects were the most frequent appeared in 14 patients (26%), severe infection specifically tuberculosis appeared in 2 patients (3.6%), allergic effects were severe in only one case (anaphylactic shock), finally the secondary cutaneous lesions of Anti-TNF were observed in a single patient (extensive psoriasis). Severe adverse reactions led to permanent discontinuation of Anti-TNF in 24.1% of cases.

The use of anti-TNF treatment is likely to generate numerous undesirable effects, hence the advantage of respecting the recommendations relating to the assessment before any treatment with biotherapy and of making regular clinical follow-up during treatment with a meticulous clinical examination as well as biological monitoring in order to prevent the occurrence of these complications, and to manage them correctly once they appear.

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Introduction

Inflammatory Bowel Disease (IBD), are characterized by chronic inflammations of the digestive tract reaching exclusively the rectum and colon for Ulcerative Colitis "UC" and whole digestive tract with a predilection for the ileo-cecal region for Crohn Disease "CD". Anti-TNF drugs occupy an important place today in the therapeutic arsenal of IBD. They have revolutionized Traitement of IBD and have opened a new era where we can hope for better control or even a cure. These molecules are not without risks, in particular infectious events, and their use requires rigorous and repeated monitoring of patients. Despite improvement in the quality of life in patients under Anti-TNF both physically and psychologically, these biological treatments have numerous undesirable effects, some of which are paradoxical.

The aim of this work is to study the tolerance of biotherapies in patients with IBD seen following the consultation of IBD, or hospitalized in the gastroenterology department of the CHU Mohamed VI of Marrakech, and to list the main adverse effects occurring in our patients, their moment of occurrence, their management, and finally to establish a practical approach for the management of these side effects.

Patients and Methods

We carried out a prospective study on a cohort of fifty-four patients with chronic inflammatory bowel disease, treated by biotherapy, in the gastroenterology department of CHU Mohamed VI over a period of 48 months.

We included in our study all patients with Crohn's disease or ulcerative colitis, whose diagnosis was made on clinical, endoscopic, morphological, histological, and biological arguments. Patients received at least three infusions of Infliximab 5 mg / kg or 10 mg / kg at weeks 0, 2, 6, and then every eight weeks. And at least 4 injections of Adalimumab subcutaneously at a starting dose of 160 mg followed by 80 mg in the second week, then every two weeks. Contraindications have been strictly respected.

Results

223 new patients presented with a chronic inflammatory bowel disease selected on clinical, biological, morphological and histological criteria were treated in our department of gastroenterology, 54 patients were treated with biotherapies immediately (Top down) or after failure of conventional treatment (Step up) with an incidence of 24.2%. Twenty nine of the 54 patients in the study presented adverse effects of treatment, with a prevalence of 53.7. 17 patients were male and 37 patients female, a sex ratio of 0.45 in favor of women. Of these patients, 7 male and 22 female experienced adverse drug reactions. 51 patients were non-smokers, 2 were quit smokers and 1 was still smoking at the time of introduction of Anti-TNF. We have reported 8 cases of familial IBD (5 MC, 3 UC). A history of pulmonary tuberculosis was found in 1 of our patients and a tuberculous contagion in 2 patients. Of the 54 patients, 38 patients had a Crohn's disease, while the UC was reported in only 16 patients. Ileal-caecal (L3 of Montreal) and anoperineal were most frequent locations of Crohn's disease. Penetrative (B3) phenotype was predominant, present in 22 patients (57%), followed by the stenosing phenotype (B2) in 8 cases (21%), inflammatory (B1) in 2 cases (5%), and finally the phenotype was mixed in 6 cases either 15.8%. The distal rectosigmoid location was predominant in our UC patients found in 8 cases. Almost all of our UC patients were treated with salicylated derivatives (96%). Almost all of our patients (98%) received corticosteroids; antibiotic for a digestive indication (abscess, collection) was prescribed in more than 46% (25 cases). A significant number of our patients received immunosuppressive therapy (53 cases or 98%), based on azathioprine in 24 cases (44.4%), 6-mercaptopurine in 21 cases or 38.9%, ciclosporin in 6 cases (11%), and methotrexate in only 2 cases (3.7%). The average duration of treatment was 16 months. Eighteen patients were operated either immediately or during the course of their disease before the introduction of biotherapy, 4 abscess drainages were performed in patients with adverse events under biotherapy.

In our study, biotherapies were prescribed for the following indications:

- ➢ Crohn's disease: (38 patients)
  - ✓ Active Active disease intolerant of conventional treatments in 12 cases.
  - ✓ Penetrative disease (fistulas other than LAP) in 11 cases.
  - ✓ Disease with severe joint manifestations in 5 cases.
  - ✓ LAP 10 cases.

- ➢ Ulcerative colitis: (16 patients)
  - ✓ Ulcerative colitis with failure of conventional treatments (corticosteroid resistance, corticosteroid dependence, and failure with azathioprine) 14 cases (26%).
  - ✓ Severe acute colitis 2 cases (3.7%)

Pre-therapeutic assessment was requested from all our patients. Anti-CMV IgM were positive inone patient who rwas treated after confirmation by PCR with Acyclovir, an IDR + was found in 2 patients who were subsequently put on anti-bacillary treatment before starting biotherapy. And there were no contraindications to the administration of anti-TNFα in other patients. Screening tests for latent tuberculosis including tuberculin IDR, chest x-ray and Quantiferon were negative in patients with tuberculosis secondary to biotherapy.

Out of 54 patients, 44 were treated with Infliximab (81.5%) (42 patients received Infliximab, 2 patients the biosimilar of Infliximab). At a dose of 5 mg / kg at week 0,2,6; then every eight weeks. The average number of infusions for all patients was 14 with extremes ranging from 4 to 24. The average duration of intake was 9.35 months (1 to 20 months).

Eight (08) patients were treated with Adalimumab (14.8%). At a dose of 160 mg at S0 and 80 mg at S2, then 40 mg every two weeks. The average number of injections was 9.5 with extremes ranging from 6 to 13. The average duration of injection was 4 months with extremes ranging from 2 to 6 months (Figure 1).

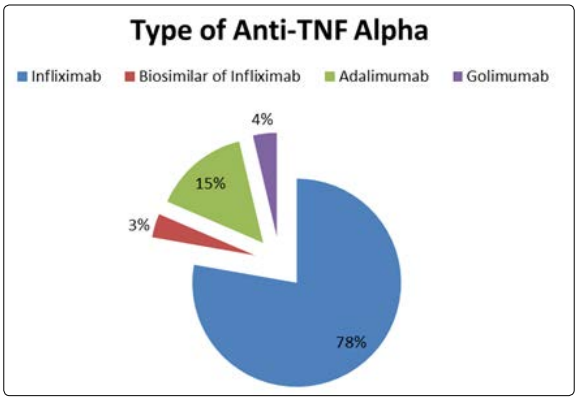

Figure 1: Distribution of patients according to the anti-TNFα used

Two (02) patients received Golimumab (3.7%). At a dose of 200 mg (2 injections of 100 mg) then 100 mg after 2 weeks. Thereafter the administration rate is one injection every 4 weeks. The average number of infusions for all patients was 3 with extremes ranging from 2 to 4. The average duration of administration was 6 weeks (2 to 10 weeks).

Forty-six patients out of 54 (86%) received combination therapy (biotherapy treatment was combined with azathioprine (2.5 mg / kg), including 19 patients who had a severe intolerance to treatment (35%).

The 54 patients with IBD responded well to induction treatment, after a clinical-biological evaluation, the Harvey Bradshow score for CD and Mayo score for CR, two weeks after the end of induction treatment. However, 3 patients did not respond well to treatment.

At the end of our study, only 42 patients (77.8%) had received maintenance treatment, the other 12 patients (22.2%) having received only induction therapy. Of these 12 patients who did not receive maintenance therapy, 9 had presented side effects of Anti-TNF therapy, the response to maintenance therapy with biotherapy is shown in Figure (2).

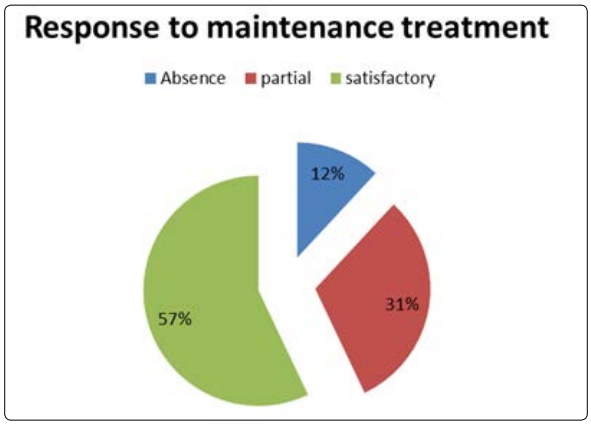

Figure 2: Distribution of patients according to response to treatment

Biotherapy treatment was well tolerated in 25 patients with IBD (46.3%), of these patients 19 patients were on Infliximab, 4 on Adalimumab, and 2 on Golimumab (Figure 3).

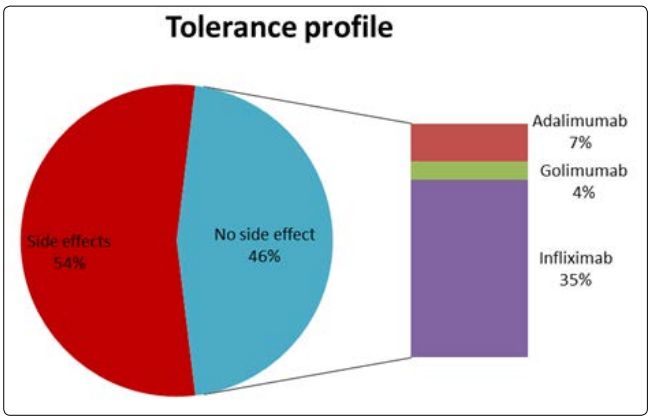

Figure 3: Distribution of patients according to the tolerance profile for biotherapies

Twenty-nine patients (46%) experienced adverse effects; several adverse effects may be associated in the same patient (Figure 4).

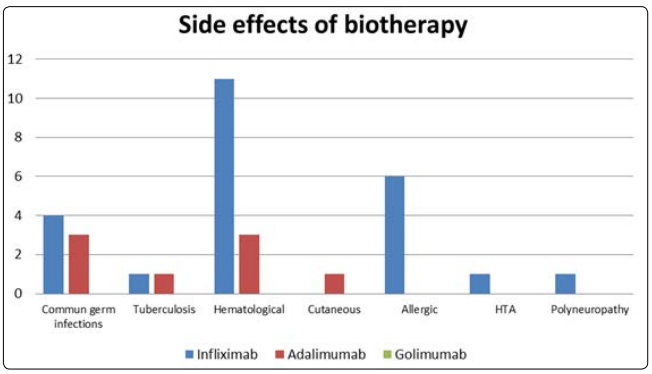

Figure 4: Distribution of undesirable effects according to the biotherapy molecule used

Hematologic and infectious complications were the most frequent in our patients, four types of hematological disorders appeared in 14 patients on biotherapy (26%), and were distributed as follows: 10 cases of hypochromic microcytic anemia, appeared after 4 cures on average for 8 patients on Infliximab and 2 cures on average for 2 patients on Adalimumab, 2 cases of neutropenia on combination therapy, appeared after 2 cures in one patient and after 6 cures in the other patient on Infliximab, 1 case of thrombocytopenia 3 courses of Infliximab at a dose of 5 mg / kg, 1 case of thrombocytosis appeared in a patient on combination therapy, after the 5th course of Infliximab at a single dose, the responsibility of thiopurines in these hematological accidents has been ruled out by a dosage of TPMT . Regarding the infectious complications, they were divided into infections with a common germ which did not necessitate to stop treatment, noted in approximately 9.25% of patients (5/54 with 3 cases of urinary infections with E. Coli, 1 case of non-tuberculous bronchopulmonary infection, 1 case of gastroenteritis, 1 case of oral candidiasis), and opportunistic infections and tuberculosis which occurred in 2 patients (3.7%): one patient with pulmonary common tuberculosis appeared after 6 injections of Adalimumab (40 mg / kg), and multifocal tuberculosis in a patient appeared 3 weeks after 3 injections of Infliximab (Week 6) at dose of 5 mg / kg.

Cutaneous adverse event (generalized psoriasis) was noted in one patient (2%), the effect appeared after 4 cures of Adalimumab.

An allergic reaction occurred in 4 patients (7.4%): An anaphylactic reaction appeared in one patient after 3 cures of Infliximab at a single dose of 5 mg / kg, and 3 cases of hives with pruritus were appeared in 3 patients taking Infliximab after 2, 3 and 6 injections at a dose of 5 mg.

A hypertension peak appeared in an unknown hypertensive patient after 8 injections of Infliximab at a dose of 5 mg / kg.

A Peripheral axonal polyneuropathy, occurring at sixth week in a young patient put on Infliximab at a dose of 5 mg / kg, followed for ulcerative colitis in pancolitis and resistant to first line treatment.

Occurrence of side effects had an impact on poursuite of treatment in our study: an optimization by reduction of the doses of drugs and spacing of the cures was recommended in a single patient (3.4%), a stop then a reintroduction of treatment was indicated in 8 patients (27.5%), the mean reintroduction time was 6.5 weeks [1-12 weeks], treatment was stopped permanently in 7 cases including patients with severe side effects (anaphylactic choc and extensive psoriasis) (24.1%), a Switch of Infliximab by Adalimumab was indicated in a single patient (3.4%), Anti-TNF therapy was continued in 12 patients (41.4%) with adverse effects that did not require the cessation of biotherapy, their management consisted of specific treatment for the adverse reaction (Figure 5).

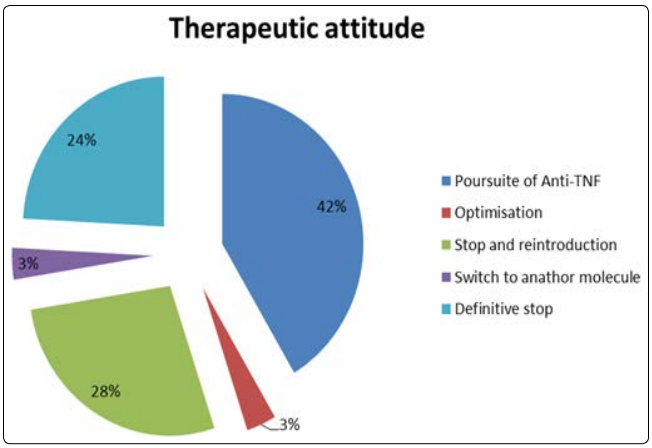

Figure 5: Impact of the adverse effect on the management of patients receiving biotherapy

The specific treatment for the side effects had consisted of: A probabilistic antibiotic therapy then adapted to antibiogram, evolution in this groupe was then favorable, antiviral treatment for patients with viral infection, antimycotic agents for candidiasis, anti-bacillary treatment for 6 months, and 9 months, iron therapy or an iron infusion for injection in the event of iron deficiency anemia, corticosteroid therapy with antihistamine in allergic reactions, and corticosteroid therapy in the case of extensive psoriasis.

The median duration of resolution of the undesirable effect was: 6 months for tuberculosis, the resolution of hematological disorders was done in 3 weeks on average, the duration of resolution of psoriasis was 2 months, infections with banal germ resolved on average in 15 days, allergic reactions resolved on average in 2 weeks.

Discussion

Anti-TNF Alpha are monoclonal antibodies with specifically recognizing of soluble and transmembrane forms of TNF, to bind to them by forming stable complexes, and thus to inhibit its action. They currently have validated indications in chronic inflammatory

bowel disease (IBD).

All anti-TNFα agents expose to similar risks and seem to have the same tolerance profile, the side effects observed being generally class effects [1].

In fact, anti-TNFα agents increase the risk of developing an opportunistic infection or not, mainly pulmonary (with the risk of tuberculous reactivation) skin and urine. Tuberculosis is the most commonly described infection regardless of anti-TNFα. The risk of occurrence of opportunistic infections, serious bacterial infections and viral reactivation (shingles, recurrent herpes, hepatitis B) remains a major concern in patients treated with anti-TNFα [1].

This is why before considering treatment with anti-TNFα, it is prudent to look for infections (dental, ENT, urine) and to look for an abscess (in the presence of fistula). It is also recommended to perform a gynecological examination with a smear to rule out the presence of papillomas virus. A biological examination with an NFS, an assay of hepatic enzymes, associated with HIV, HBV, HCV and VZV serologies (after patient agreement) may supplement the assessments preceding the initiation of anti-TNFα treatment.

In randomized controlled trials, approximately 25 to 40% of patients on maintenance TNFα therapy will develop side effects or a loss of response to treatment. These events most often occur within 6 months of the initiation of treatment. In an observational study of 614 MC on IFX, 10.9% of patients did not respond initially to treatment, and during the median follow-up of 55 months, 12.6% of patients had to stop treatment for adverse effects, 21.6% had a loss of response [2].

In the initial experience of the first 500 patients treated with Infliximab at the Mayo Clinic, 41 infections linked to the treatment of them were reported [3]. In 34 cases (83%), these were non-opportunistic bacterial infections (pneumonia, septicemia, intra-abdominal or ano-perineal abscess, cellulitis, urinary tract infection, etc.). since four of these patients died.

The alarm signal was launched in 2001 by Kaene et al. [4], reporting 70 cases of tuberculosis occurring under IFX listed between 1998 and 2001 by the FDA's AERS (Food and Drug Association's Adverse Event Reporting System). Among these 70 cases, 67% were treated for rheumatoid arthritis (RA) and 26% for Crohn's disease; and 64/70 tuberculosis occurred in countries with low endemicity for tuberculosis. The average reporting interval was 12 weeks (1-52 weeks).

In our study, we had 2 cases of tuberculosis occurring under Anti-TNF, one case of CMV infection and one case of herpes simplex virus infection, the evolution was favorable under specific treatment and the resumption of Anti-TNF was made without incident.

In terms of frequency, hematological side effects come after infectious complications, it is a severe complication of treatment with biotherapy, it can lead to neutropenia, which is the most frequently encountered, thrombocytopenia, anemia or even pancytopenia. This complication can be severe and can engage patient's vital prognosis, particularly in case of sepsis or hemorrhage. TNFα is part of a complex network of cytokines that control hematopoiesis; it stimulates G-CSF, CSF-1, EPO, SCF and has an inhibitory action on GM-CSF and IL3; this is how anti-TNFα could block cell differentiation [5,6]. In our series, 4 types of hematological disorders appeared in our patients, an incidence of 7%, which agrees with the data in the literature.

Anti-TNF alpha can also induce paradoxical effects. The term paradoxical side effect induced by this therapeutic class is used to designate the appearance of a condition usually cured or improved by anti-TNFα agents. The most characteristic example is the psoriasiforme rashes under anti-TNFα, while several molecules targeting this cytokine are currently approved and marketed in the treatment of moderate to severe plaque psoriasis [7,8]. In our series, we report a single case of a paradoxical generalized psoriasis, the evolution of which was favorable after stopping Adalimumab (Swap to Vedolizumab) and putting the patient on corticosteroid therapy.

Hypersensitivity reactions have been described as well as allergies; Immediate allergic reactions are seen with Infliximab in 15-20% of patients [9]. These reactions occur at the start of treatment, during or within two hours of the infusion. Patients in this case presented fever, chills, nausea, headache, pruritus, hives, chest pain, dyspnea, hypertension peak. More rare reactions such as hypotension, bronchospasm or shock are less common and can be life-threatening. There may also be delayed hypersensitivity reactions that occur 3 to 12 days after the infusion. They are manifested by arthralgia, myalgia, fever, pruritus, rash, swelling of the face or hands, headache, painful discomfort when swallowing [10].

In our cohorte, we had one case of anaphylactic shock requiring discontinuation of treatment and 3 cases of hives.

Neurological complications are not exceptional during treatment with Anti-TNF, a case of demyelination has been observed in a 19-year-old woman treated with Infliximab for CD, clinical signs such as numbness of the extremities having started 2 weeks after a third infusion [11]. Another case was reported in the Accent II trial [12]. In practice, the administration of Infliximab is not recommended in patients with a personal or family history of multiple sclerosis and the occurrence of neurological signs suggesting demyelination must suspend treatment and request additional explorations (MRI). In our series we did not have a case of demyelination; on the other hand we had a case of axonal senstivo-motor polyneuropathy in a patient on Infliximab occurring in a young patient treated with infliximab for UC.

Several cases of cancer and lymphoma have been reported in patients with CD treated with Infliximab [13-17]. Most were also on immunosuppressants and the accountability for Infliximab has not been established. The frequency of neoplasias in clinical trials and in the postmarketing experience is not higher than expected, we have reported no cases of neoplasia in our cohort [14].

Conclusion

The follow-up of patients under anti-TNFα is based on evaluation of their effectiveness, namely obtaining "mucosal healing", evaluation of the severity of intestinal damage by carrying out endoscopic examinations, and radiological, as well as evaluation of prescribed molecule's tolerance since certain cases of major intolerance impose the definitive stop of the treatment. The prevention of the occurrence of adverse effects during treatment with anti-TNFα is essentially based on a careful clinical examination as well as regular biological monitoring in order to look for possible complications.

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