Original Article

Serious Infections in Chronic Inflammatory Rheumatic Disease Patients Treated with Immunosuppressive Drugs at Douala General Hospital – Cameroon

Infections sévères sous traitement immunosuppresseur chez les patients souffrant de rhumatismes inflammatoires chroniques à l'Hôpital Général de Douala

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ABSTRACT

BACKGROUND

There is increasing use of immunosuppressive drugs (ID) in sub-Saharan Africa as new indications emerge in this region, known for its high infection rates. Few data are available on infectious complications of ID in chronic rheumatic diseases (CRD) in Africa

OBJECTIVES

To describe the pattern of serious infections (SI) in CRD patients treated with ID in the Douala General Hospital, Cameroon

PATIENTS AND METHODS

After prior ethical clearance, we reviewed medical records of adult patients treated with ID for at least 6 months in the rheumatology unit of the Douala General Hospital from January 1999 to December 2009. The types of ID, dosage, and treatment duration as well as the indication were recorded. All cases of serious infections were identified. SI were defined as requiring hospitalization, intravenous antibiotic, withdrawal of the drugs or resulting in death.

RESULTS

Sixty-four patients (43 females and 21 male) were enrolled. Indications for use of ID included rheumatoid arthritis, systemic lupus erythematosus and dermatomyositis. ID used included Prednisone (used in all the patients), Methotrexate, Cyclophosphamide, and Azathioprine. Seventeen (26.6%) patients developed at least one SI: pulmonary tuberculosis (n=5), non-tuberculous pneumonia (n=6), febrile enteritis (n=5), and upper respiratory tract (n=2). Five patients presented more than one infection. Infections were increased for patients aged more than 60, cumulated dose of Prednisone more than 700 mg, combination of prednisone and Methotrexate.

CONCLUSION

Pulmonary infections are frequent in CRD patients treated by ID. Prospective studies are needed to better evaluate the burden and risk factors of this complication in sub-Saharan Africa

KEY WORDS: chronic rheumatic disease; infections; immunosuppressive therapies.

RÉSUMÉ

INTRODUCTION

Le risque d'infections sévères (IS) est augmenté sous traitement immunosuppresseur (TI), chez les patients souffrant de rhumatismes inflammatoires chroniques (RIC).

OBJECTIF

Identifier et décrire les aspects cliniques des IS chez les patients atteints de RIC et traités par immunosuppresseurs. A l'Hôpital Général de Douala.

METHODOLOGIE

Etude transversale descriptive incluant tous les patients souffrant de RIC suivis à l'HGD de janvier 1999 à décembre 2009 et traités par TI pendant au moins 06 mois. Etaient recueillis et analysés : le type, la durée, la dose et l'indication du TI ; la survenue d'une IS. L'IS était définie comme infection nécessitant une hospitalisation, un traitement antibiotique par voie parentérale, l'arrêt du TI, et/ou responsable du décès du patient.

RESULTATS

64 patients (43 femmes et 21 hommes) ont été inclus. Les RIC recensés étaient : Polyarthrite rhumatoïde, lupus érythémateux systémique et dermatomyosite. Les TI utilisés comportaient : Prednisone (n=64) ; Méthotrexate (n=49) ; Cyclophosphamide (n=7) ; azathioprine (n= 3).
Treize (25,5%) patients ont développé au moins une IS ; les IS recensées étaient : tuberculose pulmonaire (n=7), pneumopathie non tuberculeuse (n=7), entérite fébrile (n=5), infections des voies respiratoires hautes (n=2). Les infections étaient plus fréquentes chez les sujets de plus de 60 ans, une dose cumulée de prednisone >700 mg, l'association méthotrexate et prednisone. Cinq patients ont développé plus d'une IS.

CONCLUSION

Les IS pulmonaires sont fréquentes chez les patients souffrant de RIC et traités par TI. La prévention et la prise en charge des complications liées à ces traitements sont essentielles. Des études prospectives sont nécessaires en Afrique où le contexte infectieux endémique pourrait induire une augmentation du risque infectieux lié aux TI.

MOTS CLÉS **:** rhumatismes inflammatoires chroniques ; infections ; immunosuppresseurs

INTRODUCTION

Immunosuppressive therapies (IT) are drugs that suppress the human immune response. They are currently used clinically as anti-rejection agents in organ transplantation to prevent rejection of transplant organs (alloimmunity) and for the treatment of patients with lymphoproliferative disorders and systemic autoimmune diseases (autoimmunity) [1]. Autoimmunity appears to develop when immune surveillance fails and the patient's own cells are mistaken for foreign cells. Autoimmunity can involve the production of autoantibodies from B-cells against specific tissues or the activation of cytotoxic T-cells against a specific tissue e.g. synovial membrane in rheumatoid arthritis [2]. ID constitute the first line of disease-modifying drugs used in the treatment of chronic inflammatory rheumatic diseases. Unlike the treatment of transplant rejection, which is often highly specific, treatment for autoimmune diseases may involve broad non-specific immunosuppression. Broad suppression of immune cell function often leads to numerous adverse effects particularly the failure of the organism's defense mechanisms against infectious pathogens [1,2,3]. Patients receiving immunosuppressive therapies have a heightened risk of infections including those caused by opportunistic organisms and various fungi, which are often difficult to treat. Infectious complications of these drugs are well documented in high-income countries [4,5].

The use of immunosuppressive drugs has increased in Africa in the last decade probably due to the availability of appropriate diagnostic tools and highly trained health personnel. Even though tropical sub-Saharan Africa provides an enabling environment for various infections, there is paucity of data concerning this specific category of infectious complications in patients on ID [6-8]. Therefore, we aimed in this study to describe the characteristics of serious infections in CDR patients on immunosuppressive drug at a tertiary health facility in Cameroon.

PATIENTS AND METHODS

After prior ethical clearance from the hospital Institutional Review Board, we reviewed medical records of adult patients suffering from CRD and treated with immunosuppressive drugs for over 6 months in the Internal Medicine Department of the Douala General Hospital, during a 10 years period (January 1999 to December 2009). Case files of CRD patients on immunosuppressive therapy for at least 6 months duration were included in the study. Baseline epidemiological information, relevant clinical data, indication of the immunosuppressive therapy, dosage and duration of the treatment, and type of serious infection were extracted. Serious infection was defined as infection requiring intravenous antibiotics, hospitalization, or withdrawal of the ID or resulting in death. Infection was considered in the presence of a germ on analysis of the relevant body specimen and suggestive clinical features. For organs difficult to access for specimen collection the diagnostic criteria were based on clinical signs and radiological findings. Screening for infection was limited to the clinical assessment of the symptomatic organ system and blood cultures in case of fever. Stool culture was performed in cases of enteritis. The diagnosis of pulmonary tuberculosis (PTB) was based on the presence of acid- fast bacilli (AFB) on at least one of three sputum samples submitted on three consecutive days for microscopic examination after staining by Ziehl–Nielsen's technique according to guidelines of the National Tuberculosis Control Program. [7].

Statistical methods: Categorical variables were presented as number (%) and continuous variables presented as mean and standard deviation. Statistical significance was considered at $p\ values < 0.05$. Data were analyzed using the Epi Data 3.1 Software

RESULTS

During the ten-year study period, case files of 64 patients fulfilled the inclusion criteria and were analyzed. The mean patient age was 54 [17 – 74] years and 61 (95.3%) patients were female. Immunosuppressive therapy administered included Methotrexate in 49 (76.6%) cases, Cyclophosphamide in 7 (10.9%); Corticosteroids monotherapy in 5 (7.8%) and Azathioprine in 3 (4.7%) of cases. Corticosteroids were used in combination with other IT in 59 (92.2%) patients. The baseline characteristics of the patients are summarized in **Table 1.**

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS

Characteristics	N=64
Age, median [interquartile range] years	54 [17 – 74]
Female/male (n)	61/3
Systemic disorders	
Rheumatoid arthritis, n (%)	49(76.6)
Systemic lupus erythematosus, n (%)	13 (20.3)
Dermatomyositis, n (%)	2(3.1)
Immunosuppressive drugs	
Methotrexate, n (%)	49(76.6)
Cyclophosphamide, n (%)	7 (10.9%)
Prednisone (alone), n (%)	5 (7.8%)
Azathioprine, n (%)	3 (4.7%)

NB: Corticosteroids was associated to another IT in 59 (92.2%) of patients

Seventeen (26.5%) of the 64 patients developed at least one serious infection. Infections recorded were pulmonary tuberculosis (n=7; 10.9 %), non-tuberculous pneumonia (n=7; 10.9%), febrile enteritis (n=6; 9.4%), and upper respiratory tract infection (sinus infection, tonsillitis) (n=2; 3.1%).

TABLE 2: IMMUNOSUPPRESSIVE THERAPIES AND INFECTIONS

Infections	MTX (n=49)	CYC (n=7)	AZA (n=3)	PRED (n=5)
No infection (n=47)	39	4	1	3
Pulmonary infection (n=14)				
TB (n=7)	4	1	0	2
Non TB (n=7)	3	2	1	1
Febrile enteritis (n=6)	3	2	0	1
Upper respiratory (n=2)	0	1	1	0

More than one infection found in five patients. PRED : Prednisone ; MTX : Methotrexate ; CYC : Cyclophosphamide ; AZA : Azathioprime ; TB : Tuberculosis

TABLE 3: FACTORS ASSOCIATED TO INFECTIONS

Factors	Presence of infection	Absence of infection
Age >60 (n=12)	6	6
Diabetis (n=5)	2	3
HIV infection (n=1)	1	0
Cumulated dose of prednisone (n=64)		
• **>700mg (n=46.71.9%)**	13(20.3%)	33(51.6 %)
• **< 700mg (n=18.28.1%)**	4(6.2%)	14(21.9 %)
Methotrexate weekly dose, mg (n= 49)	10 (20.4%)	39 (79.6%)
• **0 -9**	0	9
• **10 – 15**	8	29
• **>15**	2	1

Five (9.8%) patients experienced more than one severe infection. **Table 2** shows the distribution of infections according to type of immunosuppressive drug.

Amongst the 17 cases of infection, 6 (35.3%) patients were aged more than 60 years, 13(76.5%) received a cumulative dose of corticosteroids more than 700 mg, and 10 (58.8%) were on a weekly dose of Methotrexate of more than 10 mg.

DISCUSSION

This study revealed a high frequency of severe infections especially of the respiratory tract in patients treated with immunosuppressive drugs in an internal medicine unit of a tertiary hospital in sub-Saharan Africa. The main outcome of this study is that approximately a quarter of patients treated by immunosuppressive therapy for systemic disorders developed serious infections. There is paucity of information concerning the occurrence of serious infection in patients treated by immunosuppressive regimen in sub-Saharan Africa at the era of biologic immunosuppressive therapy in the world.

Immunosuppressive drugs, especially when used in combination with corticosteroids, in the treatment of chronic inflammatory bowel diseases, systemic lupus and rheumatoid arthritis are associated with infection. The risk of infections varies substantially with the type of disease, the older age, the dosage, the duration and the timing of the treatment [4,9,10]. We found that serious infections were more common in older patients, those with high dose of corticosteroids and with combination of methotrexate and corticosteroids, and plus high dose of Methotrexate

Corticosteroids, when used in prolonged treatment protocols, increase the chances of bacterial and fungal infections (11). The demonstration of the infectious risk associated with corticosteroids relies on observational data and on biological plausibility. This is sometimes difficult to quantify because of confusing factors such as the patients' associated conditions and immunosuppressive treatments; thus it has been suggested that infection screening may be indicated for those taking more than 10 milligrams per day (12). Therapies with corticosteroids is known to induce dose-dependent lymphocyte depletion and concomitant application of cytotoxic disease modifying drugs, as used for chronic inflammatory rheumatic conditions may lead to additive lymphocytopenia, particularly the CD4 subsets, predictive of infection (13). Total lymphocyte count nor CD4 subset were not readily available in the records of all our patients in our study.

As in some studies in sub-Saharan Africa, our results support the idea that infections are commonly found in systemic disease like RA [6] and SLE [10,11] on ID. Infections are responsible for approximately 25% of all deaths in in RA (14). The infections leading to

hospitalization and/or death are caused by pathogens such as *Streptococcus pneumoniae*; *Haemophilus influenza* and *Mycobacterium tuberculosis*, for which effective vaccination is available. RA is known to be associated with a greater than two fold increase risk of serious infection (14). This can be explained by the pathobiology of the disease itself as well as the immunosuppressive therapy. Consequently, guidelines on the use of corresponding vaccines prior to therapy, those reducing exposure to contagious contacts, screening for latent infections such as tuberculosis, minimizing exposure to corticosteroids, and targeted infection prophylaxis for high risk patients have been recommended (15). None of the patients in our current study was on chemoprophylaxis nor received vaccinations specifically prior to ID as chemoprophylaxis against Haemophilus and pneumococcal vaccine are not routinely practiced in our setting.

As in other studies, pulmonary infections were the most common infections recorded in immune suppressed patients in our study (16). Pulmonary tuberculosis accounted for 7 on the 17 infective cases. Tuberculosis is known to be frequent in immunocompromised patients, with symptoms often attenuated, leading to delayed diagnosis and high tuberculosis-related mortality (17). No tuberculosis prophylaxis was employed before or after initiation of IT in our study population as it is in real life attitude and practice in our settings. Guidelines for the use immunomodulators in the treatment of RA recommend screening for tuberculosis to detect latent or active disease [18]. Also screening for tuberculosis has been recommended in populations with great probability of developing the disease and this includes young children and immunocompromised persons (14). Tuberculin skin test and interferon-gamma release assays are designed to identify immune response against mycobacterial antigens (14). Tuberculin skin test may not be useful for diagnostic purposes in our environment because BCG vaccination is part of the national immunization program during childhood in sub-Saharan Africa [19]. However, interferon–γ–release assays, not currently available in Cameroon, may be useful to differentiate active tuberculosis from false-positive tuberculin skin test in patients with a history of BCG vaccination [18,19].

The main limitation of this study is its retrospective design, with lack of total lymphocytes count, complete bacteriological and viral work-up, but this is a reflection of the reality of a healthcare center in sub-Saharan Africa. Also, the limited number of patients made comparative statistical analysis and generalization of results difficult. In spite of these limitations, our results represent baseline information that may be used to impact patient care in the local setting, and serve for future larger prospective studies.

CONCLUSION

This study has revealed a high frequency of serious pulmonary infections in patients treated by immunosuppressive drugs for CRD. The rate of pulmonary tuberculosis in this study may constitute an argument for systematic chemoprophylaxis against TB in these patients. In the world era of biologic ID, we urgently need prospective studies to better evaluate the risk of infection related to the use of immunosuppressive therapy in sub-Saharan Africa, to determine risk factors associated and to evaluate the cost-effectiveness of chemoprophylaxis and vaccinations in this patient population.

CONFLICT OF INTEREST

None to declare.

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