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ORIGINAL ARTICLE

Cytomegalovirus, inflammatory bowel disease, and anti-TNFα

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Abstract
Background and purpose Anti-TNFα agents emerged in inflammatory bowel disease (IBD) as an effective option in situations that, otherwise, would be refractory to medical therapy. Cytomegalovirus infection may present with a high spectrum of manifestations and lead to high *morbidity and mortality*. However, its clinical significance in IBD course remains unknown and data on its association with anti-TNFα are limited.
Aims This study aims to evaluate cytomegalovirus (CMV) infection/disease in patients with IBD treated with anti-TNFα; if possible, possible risk factors associated with CMV infection/disease in IBD patients under anti-TNFα as well as the influence of CMV infection/disease in IBD course would be determined.
Methods During three consecutive years, all IBD patients starting infliximab in our department were included. Cytomegalovirus status before anti-TNFα was evaluated. Data regarding IBD, therapeutic and IBD course after infliximab, were recorded. CMV analysis was performed with polymerase chain reaction (PCR)-cytomegalovirus in peripheral blood and colonoscopy with biopsies (histopathology/immunohistochemistry).
Results We included 29 patients: female—83%; Crohn's disease–51.8%, ulcerative colitis—44.8%, non-classified colitis—3.4%; 23 cytomegalovirus seropositive. Median follow-up: 19 months (3–36). During follow-up, 14 patients were under combination therapy with azathioprine and 5 did at least 1 cycle of corticosteroids. Twenty-one patients responded to infliximab. We registered 8 exacerbations of IBD. Four patients discontinued infliximab: none had CMV infection. We documented 1 case of intestinal cytomegalovirus infection—detected in biopsies performed *per* protocol in an asymptomatic UC patient, who responded to valganciclovir without infliximab discontinuation.
Conclusions Infliximab, with/without immunosuppression, does not confer an increased risk of (re)activation of cytomegalovirus. Cytomegalovirus was not responsible *neither for significant morbidity nor mortality* in IBD.

Keywords Cytomegalovirus infection · Inflammatory bowel disease · Anti-TNFα agents · Immunomodulators

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Introduction

Anti-TNFα agents emerged in inflammatory bowel disease (IBD) as an effective option in situations that, otherwise, would be refractory to medical therapy [1, 2]. However, an increased susceptibility to bacterial, mycobacterial, and fungal infections has been associated with these agents [3–12]. The relationship between anti-TNFα therapy and viral infections is, however, less known.

Cytomegalovirus (CMV), a *Herpesviridae* family member, causes a common viral infection with frequencies varying between 40 to 100% of adults, depending on the age and geographical location [13, 14]. Generally, CMV infections are asymptomatic or associated with mild non-specific and

self-limited manifestations [15]. It has, however, been documented in rare cases of severe [16–18] and systemic primary or recurrent CMV infection with gastrointestinal or liver [14], neurological, pulmonary, ocular, or vascular involvement [19], normally in situations of acquired cellular immunity defects (e.g., post solid organ or bone marrow transplantation). IBD, with a predominance of ulcerative colitis (UC), has also been associated with CMV infection [17, 18, 20], with several reported cases of CMV present in the colorectal mucosa—up to 21 to 34% of the UC patients [21]. Corticosteroids and/or immunosuppressors have been associated with this risk of infection [13, 22–25]. However, the clinical significance of this infection in IBD course remains still under discussion. On the one hand, some authors suggest that CMV works only as a "bystander innocent," reflecting a remote infection of the involved mucosa, without significant impact on patients outcome [21]: others point to a worsening of the underlying disease in CMV presence [16, 18, 26, 27], counting with several cases of refractoriness to steroids or immunosuppressive therapy [21]. Data on the association of anti-TNFα therapy with CMV infection/disease and subsequent involvement of CMV in IBD prognosis are, however, even more scarce [28].

With this study, we aimed to evaluate CMV infection/disease in IBD patients treated with anti-TNFα. Additionally, if possible, possible risk factors associated with CMV infection/disease in these patients would be determined as well as the influence of CMV infection/disease in IBD course.

Material and methods

This was an observational cross-sectional/longitudinal study held in the Gastroenterology Department of the tertiary hospital Centro Hospitalar e Universitário de Coimbra (CHUC). During 1 January 2012 and 31 December 2013, all IBD patients followed in our Gastroenterology Department who started infliximab (IFX) were included in the study. Before starting anti-TNFα therapy, an evaluation for cytomegalovirus status was made. All patients were treated with anti-TNFα according to standard therapy protocol (0, 2, and 6 weeks and every 8 weeks thereafter). The patients were followed until 31 December 2015. A reevaluation regarding CMV status was conducted after at least 1 year of follow-up.

We analyzed the following parameters:

(a) Disease data and therapy before IFX: type, location, extent behavior (using Montreal classification), severity (through Truelove and Witts criteria in UC [1] and Harvey-Bradshaw activity index in Crohn's disease—CD [2]), corticosteroid dependence, and corticosteroid resistance (as defined in international guidelines [1]). Therapy included per os/topical 5-ASA, per os/intravenous corticosteroids, cyclosporine, and azathioprine/6-mercaptopurine/methotrexate.

(b) IFX data: indication for the introduction (induction and remission maintenance in moderate to severe CD, induction and maintenance of remission in moderate to severe UC, induction and maintenance of remission in severe UC resistant to intravenous steroids or treatment of fistulizing CD [1, 2]), dose, interval between infusions, and use of other therapeutics (corticosteroids/immunosuppressants).

(c) IBD course after IFX: *IFX response* was defined as the ability to stop and remain off corticosteroids while not requiring additional therapy for active disease. We registered a worsening of the disease despite IFX (defined by the presence of symptoms needing a anti-TNFα escalating, either increasing its dose or decreasing its infusions interval, and/or association with steroids and/or immunosuppression), IFX suspension (lack of efficacy, side effects, other reason), hospitalization, IBD-related surgery for disease activity despite IFX, and death as loss of IFX response.

(d) CMV infection/disease: All patients were initially assessed by CMV serology (CMV-immunoglobulin G—CMV-IgG—and CMV-immunoglobulin M—CMV-IgM) previous to anti-TNFα initiation to evaluate CMV status. During follow-up, after IFX introduction, CMV status was reassessed. Given the limitations of the determination of CMV infection by serological methods, in the presence of seropositivity for CMV (defined in the presence of positive CMV-IgG with or without positive CMV-IgM), CMV status was determined through polymerase chain reaction (PCR) technique in real time with Q-CMV Real-Time reagent Complete Kit (Nanogen) and automated extraction apparatus in QIAcube (Qiagen®) with subsequent molecular amplification of CMV and through endoscopic evaluation with tissue samples of ileocolonic mucosa (three to six biopsies through the colorectal mucosa) and demonstration of CMV infection in the bowel by conventional histopathology, on hematoxylin/eosin staining and immunohistochemical stains. The categorization of IBD patients regarding CMV status followed a widely accepted classification [29]: *CMV infection*, defined in the presence of CMV in active replication in a body fluid (peripheral blood) or in a tissue sample (colon), in a patient with no symptoms or signs of systemic or local CMV infection (fever, lymphadenopathy, anorexia, leukopenia, thrombocytopenia, hemophagocytosis, or intestinal or extraintestinal complications); *CMV disease without intestinal involvement*, characterized by the presence of CMV infection by the above listed methods, combining with symptoms and signs of systemic infection but without intestinal affectation; *CMV disease with bowel*

involvement, defined in the presence of CMV infection by the methods listed above, associated with clinical signs (fever, anorexia, weight loss, lymphadenopathy, abdominal pain, splenomegaly, diarrhea, hematochezia, tenesmus, megacolon, decay rapid clinical), endoscopic findings, and demonstration of CMV infection in the intestine.

(e) Therapy for CMV infection: ganciclovir, valganciclovir, or foscarnet.

(f) Statistical analysis: The values calculated to characterize the study population were expressed as mean ± standard deviation or median + interquartile ranges, depending on the quantitative variables being symmetrical or not. Similarly, qualitative variables were expressed as number of cases and as a percentage. Statistical analysis was performed using the SPSS© 20.0 software.

(g) Ethical aspects: The proposed study protocol complies with the tenets of the Declaration of Helsinki, meets the ethical investigational principles in human subjects of the Ethics committee in our institution, and was approved by the department's institutional review board. The authors safeguarded data collection from the physician subject to professional confidentiality and ethical code and the anonymity of the participants, by the assignment of a unique identification number that was only accessible to the investigators. All collected data were treated, published, and presented in a grouped manner, in a way that the participant was not identified.

Results

(a) IBD patients under IFX: 29 IBD patients starting IFX were consecutively included. The characteristics of these patients and their diseases are listed in Tables 1, 2, and 3.

(b) IFX response: The patients were followed during a median of 25 months (3 to 48 months). During the follow-up time, 14 (48%) of the patients were under combination therapy with azathioprine and 5 did at least 1 cycle of corticosteroids. Twenty-one patients maintained response to IFX (72.4%). The 8 disease exacerbations are explained in Table 4. In total, 4 patients discontinued IFX (the reasons are listed in Table 5). None of the patients who suspended IFX had CMV infection.

Table 1 Characteristics of our population study

IBD patients characteristics	Number and percentages
Female sex	24 (83%)
Type of IBD: CD/UC/non-classified colitis	15 (51.8%)/13 (44.8%)/1 (3.4%)

Table 2 Characteristics of CD patients

CD patients characteristics	Number and percentages (N = 15)
Mean disease duration (years)	7.6 ± 7.9
Location of disease	L1–3/L2–8/L3–2/L4–2 p–7
Behavior of disease	B1–4/B2–2/B3–9
Previous therapeutics:	
- 5-ASA	6
- Corticosteroids	12
- Azathioprine/methotrexate	13/1
- Surgery	4
Indication for anti-TNFα in CD:	
- Induction and remission maintenance in moderate to severe CD	10 (64.3%)
- Treatment of fistulizing CD	5 (35.7%)

(c) CMV infection and disease: Almost all of the patients (n = 23) were CMV seropositive prior to IFX (80%–CD, 83%—UC). Blood PCR-CMV was performed to all patients: zero CMV infection. All patients were also evaluated through colonoscopy and intestinal biopsies. We only registered one case of intestinal CMV infection. It was a 51-year-old female patient, seropositive for CMV, with a 1-year duration of UC corticosteroid resistant who started IFX. She had initial partial response to anti-TNFα therapy. A colonoscopy performed later for reevaluation showed severe disease with spontaneous bleeding and ulceration in the colon (Mayo score—3) and biopsies, using hematoxylin/eosin staining and immunohistochemical stains, which documented CMV infection. The patient underwent therapy with valganciclovir without discontinuation of IFX. Subsequent examination confirmed absence of colonic inflammation and CMV infection. To date, the patient is stable under 5-ASA and IFX.

Discussion

The association between CMV and IBD was described long ago. The first case report dates from 1961, when Powell et al. [30] described a patient with UC and cytomegalic inclusion disease. Since then, questions remain about the role of CMV in IBD patients: does CMV reactivation exacerbate the disease in patients with established IBD? Or is it just a consequence of IBD activity and its treatment, with CMV acting as only an innocent bystander? [26, 31, 32].

Table 3 Characteristics of UC patients

UC patients characteristics	Number and percentages ($N = 13$)
Mean disease duration (years)	7.9 ± 8.1
Location of disease	E1–2/E2–4/E3–7
Severity of disease	S2–4/S3–9
Previous therapeutics:	
- 5-ASA	13
- Corticosteroids	13
- Azathioprine	7
- Cyclosporine	2
Indication for anti- TNFα in UC:	
- Induction and maintenance of remission in moderate to severe UC	7 (54.5%)
- Induction and maintenance of remission in severe UC resistant to intravenous steroids	6 (45.5%)

CMV diagnosis In this study, we included patients with previous evaluation of CMV seropositivity through serology in order to identify, through IgG class, prior exposure history to CMV and the consequent risk of displaying primary infection (IgG negative) or reactivation/reinfection (IgG positive). However, serological testing has poor utility for diagnosing active infection or disease, as IgM are often absent or delayed in reactivation or reinfection especially in immunocompromised patients [29]. For this reason, we adopted the direct detection of CMV through PCR, which allows the quantification of CMV load. It is a very sensitive and specific test with in clinical practice [29]. Antigenemia assay was not an option, as it does not differentiate between latent infection and active disease [33]. To complement the diagnosis of CMV infection in the tissue, we used bowel specimens, stained by hematoxylin and eosin for the detection of CMV-infected cells, added to the use of monoclonal antibodies directed against CMV antigens by immunohistochemistry, which increases the diagnostic sensitivity by about 30% [29]. PCR-DNA amplification assay in colon mucosa is not available in our hospital, and viral culture is no longer used in clinical practice, as it was very time consuming.

CMV prevalence in IBD patients Most of our IBD patients, both UC (83%) and CD (80%), were CMV seropositive (positive IgG-CMV). Overall, true CMV prevalence is unknown in IBD patients. Most of studies use selected patient groups and different types of studies and diagnostic methods, so that available data include a wide range of prevalence. Latest data report rates from 70 [28, 33] to 90% [34] in CD and from 70 [26, 33] to 92% [34] in UC patients, percentages as high as in other populations.

Relationship between IBD patients under IFX and CMV infection/disease In our study, active CMV infection was present in only one IBD patient under IFX (3%). No progression to CMV disease was documented. Our results are similar to D'Ovidio et al.'s study [28], where the IFX was not responsible for CMV reactivation in IBD patients, and to Carmo et al.'s study [34], which states an infrequent active CMV infection in IBD patients and questions the virulence of CMV in patients with IBD.

Relationship between CMV infection and IBD course We only had one patient with UC and CMV infection and where the role of CMV in the IBD course cannot be reliably evaluated. The role of CMV in IBD is still not clear, but the clinical consequence of a CMV infection may differ between CD and UC. Although having similar CMV seroprevalences between both diseases, CMV disease is rare in CD and more frequent in

Table 4 Characteristics of IBD patients with loss of response to IFX

Patient (disease)	Location of exacerbation	Duration IFX (months)	Treatment	Infliximab suspension
1 (CD)	Intestinal	6	X IFX ➔ surgery ➔ AZA ➔ IFX again (endoscopic recurrence)	Yes (loss of response)
2 (CD)	Rectum (with rectovaginal fistula)	21	Surgery	No
3 (CD)	Cutaneous (Metastatic CD)	24	–	No (infusion interval to every 6 weeks)
4 (CD)	Peri-anal abscess	31	Surgery + AB	No
5 (UC)	Intestinal	12	AZA + CS	No (infusion interval to every 6 weeks)
6 (CD)	Intestinal + anal fistula	6	X IFX ➔ surgery ➔ AZA ➔ IFX again (anal fistula recurrence)	Yes (loss of response)
7 (CD)	Intestinal	18	CS + MTX (AZA suspended because of leucopenia)	No
8 (UC)	Intestinal	2	–	No (infusion interval to every 6 weeks + infliximab doses to 10 mg/kg)

Table 5 Reasons for IFX discontinuation

Reason for infliximab suspension	Number of patients
Loss of response	2 (patients number 1 and 6 of Table 4)
Pregnancy	1
Patient decision	1

UC [35]. The reason to this lies on the fact that in CD, the Th1 response is exacerbated, and the major cytokines (namely interferon-γ) produced are highly efficient in controlling CMV replication [29, 33]. The same does not occur with UC, where the increased Th2 response involved does not result in the production of cytokines able to control CMV reactivation [29]. The decision to institute antiviral therapy in CMV colitis is still unclear [29]. Our patient was submitted to antiviral therapy based on the presence of endoscopic and histological activity and infection and the scientific data suggesting that CMV treatment may restore the efficacy of immunomodulatory treatments and even prevent the need for colectomy [29]. As only one case of CMV infection was detected, it was not possible to determine possible risk factors associated with CMV infection/disease in IBD patients treated with IFX.

IFX influence in CMV infection in IBD patients The IBD patient continued IFX despite the CMV infection, without progression of the infection. Lavagna et al. [36] also supported the safety of IFX with respect to latent virus reactivation. In their prospective study, no systemic CMV infection (determined by blood CMV-PCR) was observed in 60 IBD patients followed during the first 14 weeks of infliximab treatment. Some authors [29] state that TNFα enhances CMV viral replication, and so, IFX could reduce the risk of CMV reactivation. European guidelines also recommend immunosuppression suspension only in case of severe systemic CMV reactivation, which did not occur in our case [37].

CMV infection influence in IBD patients under IFX IFX provided a response in a large percentage of IBD patients (72.4%). In patients without response or with flare-ups despite IFX, no CMV infection was detected. The patient with CMV infection responded to IFX despite CMV presence in the colon, even in the waiting period for starting CMV treatment. Our results are similar to D'Ovidio et al's [28], where clinical response to IFX was not influenced by CMV infection/disease. Previous study [38] has also shown that patients under anti-TNFα therapy are not at higher risk of CMV reactivation in case of flare-up.

Vantages and limitations of our study The present study, although small, was prospective, and the CMV status previous to IFX introduction was evaluated. It was performed in a tertiary center and included patients with moderate to severe disease, a subgroup of IBD patients where the risk of reactivation of CMV should be higher and more severe, which was not confirmed in our results. The detection of CMV, either from blood or from tissue, was assured by sensitive and specific diagnostic methods. From the authors' knowledge, scare are the data regarding this theme, with only one study directly assigned to a similar goal, but with a smaller population [28]. In conclusion, although CMV has been described as potentially responsible for significant clinical morbidity in IBD patients, this was not observed in our series where only one case of CMV was found. Additionally, our study shows that biological therapy, with or without immunosuppression, does not seem to confer an increased risk of (re)activation of CMV infection/disease.

Compliance with ethical standards The proposed study protocol complies with the tenets of the Declaration of Helsinki, meets the ethical investigational principles in human subjects of the Ethics committee in our institution, and was approved by the department's institutional review board.

Conflicts of interest The authors declare that they have no conflict of interest.

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