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Clinical Research in Infectious Diseases

Review Article

Cytomegalovirus in Ulcerative Colitis: Bystander or Leading Actor

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Submitted: 23 November 2016

Accepted: 05 January 2017

Published: 07 January 2017

ISSN: 2379-0636

Keywords

- Cytomegalovirus or CMV
- Ulcerative colitis or UC
- Inflammatory Bowel Diseases or IBD

Abstract

Background: The link between Cytomegalovirus (CMV) infection and Ulcerative Colitis (UC) is well known, but the exact direction of the causal relationship is difficult to assess. This uncertainty has a huge impact on therapeutic strategies, such as for the use of antivirals and the management of ongoing immunosuppression. The aim of this review is to discuss the main critical issues in this topic and find a clinically practical approach.

Databases covered: MEDLINE, EMBASE and Cochrane were searched.

Discussion: Real time PCR should be considered the best diagnostic test, both in tissue and blood, even though there are no standardized methods and no sure thresholds. CMV infections (systemic or intestinal) are more common in patients with an active severe form, while rare in the mild/inactive forms, and the prevalence is particularly high in patients with a steroid-refractory disease (above 30-40%).

There is a general lack of long-term studies on the natural history of CMV-infected UC patients. There is no evidence of an unfavorable long-term impact of CMV on the course of severe UC, but in terms of short-term prognosis, in recent years a general consensus has been growing about the unfavorable effect of CMV infection/re-activation in UC.

In the management of viremic patients a step by step, personalized approach should be preferred. As a general rule the antiviral treatment should be adopted in viremic steroid-resistant forms, receiving immuno-modulators (IM) which are generally safe, and an ongoing treatment with anti-TNF does not worsen the course of the infection. There is an indication to stop the IM therapy only if a severe systemic infection is diagnosed.

INTRODUCTION

The link between Cytomegalovirus (CMV) infection and Inflammatory Bowel Diseases (IBD), particularly Ulcerative Colitis (UC), was postulated a long time ago [1,2]. CMV is able to maintain a life-long infection in the host, even though in a latent and asymptomatic form, but sometimes when provoked by some conditions such as an inflammation or immunosuppression, it can re-activate. CMV can be isolated from a multitude of tissues, including the colon. In patients with UC the local inflammation could lead to CMV replication under a favorable "cytokine milieu" [3]. The balance between the host immune response and the virus is the critical point, so in UC where both a chronic inflammatory status and immunosuppression are often combined, this kind of opportunistic infection seems to play an important role. However, the significance of this association is still debated. CMV is quite common, with a seroprevalence (CMV IgG-positive) of 40–100 % in adults, increasing with age [4] and it is possible to detect viral products or nucleic acids in the colon mucosa of healthy people. The principle goal of the clinician is to distinguish patients with an active infection from those in which the virus is just a bystander, and if the virus has an influence in the prognosis of the disease. No unanimous consensus has emerged in recent decades, and conflicting results have been published. Even the definition of CMV infection is under scrutiny. In this review we will try to answer some questions that are highly relevant in daily clinical practice:

1- How can an active CMV colitis be detected?

2- What is the prevalence of CMV infection among patients with UC?

3- What is the real impact of CMV on the course of UC?

4- Which patients need antiviral treatment?

5- In the case of an ongoing CMV infection, is it possible to maintain an IM agent or is it mandatory to stop it?

Search methods

We reviewed the medical literature available on this topic using the MEDLINE, EMBASE and Cochrane databases. As medical headings we used "cytomegalovirus" OR "CMV" OR

"cytomegalo virus" AND "inflammatory bowel disease" OR "IBD" OR "ulcerative colitis". Both mesh terms and free searches were performed, and we selected only English-language papers.

DISCUSSION

How to detect an active CMV infection

The classical clinical scenario is a patient with massive bloody diarrhea, as a presentation of a new-onset disease, or a reactivation of an UC under IM. The first question is: is the reactivation of the UC caused by the CMV, or is it an inflammatory cause, and what is the most useful test for detecting an active CMV infection?

There is an unbelievable number of methods to detect CMV in the blood and in the colon tissue. As a general rule, the laboratory diagnosis of an active CMV infection is based on the detection of the virus or its products in the blood. Several techniques have been developed for this aim, of which the most often used are:

- Serological assays of IgG or IgM antibodies (ELISA) to CMV are not useful for the diagnosis and for monitoring the infection, but they are very helpful in screening patients at risk of reactivation.
- The detection of pp65 antigenemia in the white peripheral blood cells (WBC) was very common in the past, because it is a good marker of an active blood infection, but it is not automated and still remains a subjective analysis.
- The shell vial culture, in which the sample is centrifuged onto a single layer of cells and viral growth is measured by antigen detection methods [5]. This method is able to quantify the amount of virus in a cell culture and it is also strongly correlated to the viral replication. Nevertheless methods based on the culture have a low sensitivity in immunocompromised patients and are longer than the others.
- Real time Polymerase-Chain-Reaction (PCR) for the quantification of viral DNA has shown the most reliable results. The reaction can be used on different materials like blood, WBC, plasma, tissues, is very fast (hours), can be automated, and it is standardized.

For the diagnosis of reactivation at the colon level two kinds of quantitative diagnostic approach are available. Immunohistochemistry (IHC) is based on the detection of viral antigens on the colon tissue, and real time PCR assay. Both are considered valid methods to detect the presence of an active colon CMV infection, together with the classic histological hematoxylin and heosin (HE) staining. However, it should be underlined that real time PCR is more widespread, probably because of its simplicity and rapidity. ECCO guidelines for the diagnosis and management of opportunistic infections in IBD state: "the most commonly used technique for diagnosis of CMV infection and disease is detection of CMV DNA through PCR in tissue biopsies and in the blood" [6]. In order to increase the sensitivity of the test, the biopsies should be performed in the more ulcerated areas, because of the highest probability of finding infected cells [7]. It could also be useful to combine different histological techniques such as HE and IHC stains together with PCR on tissue. The molecular amplification of the viral nucleic acids can be considered the technique of choice, but in day-to-day clinical practice what is really important is the positive predictive value (PPV) of this test; in other words, how many times a positive result indicates the presence of a real disease. We know that only a minority of CMV infections lead to a clinical disease, which means a lower PPV for the above-mentioned tests. To increase the PPV physicians should select the right population to test: those people with the higher pre-test probability of a clinically relevant infection. Clinicians should also define thresholds of CMV DNA load. Unfortunately, there is a lack of standardization and no sure thresholds have been established. This lack of agreement and universally valid cut-off values have led to a difficult-to-assess scenario. It is not easy to make comparisons between studies, which are based on different definitions of disease, consequently it is quite impossible to find an evidence-based unanimous consensus. Generally, 10 CMV DNA copies/mg tissue (PCR real time), is considered quite sensitive [8]. A CMV-DNA load above 250 copies/mg tissue has been associated with steroid resistance with a positive likelihood ratio of 4.33 and an area under the ROC curve of 0.85 [9]. In contrast, there is no officially approved cut-off for blood detection. For the diagnosis of a systemic infection it could be more useful than a single blood detection to plot a trend of viral load in a relatively short follow-up time (e.g. 48 hours). An increasing trend is probably a good marker of active systemic infection in symptomatic UC patients, especially in some particular conditions, such as severe steroid-refractory UC. In Table (1) we have summarized the most widespread tests for the diagnosis of CMV infection in an "easy to remember" format.

What is the prevalence of CMV infection among patients with UC?

A recent systematic review identified 21 different definitions for CMV infection, 8 definitions for CMV intestinal disease, and 3 definitions for CMV reactivation [10]. It is obvious that the prevalence of the disease depends mainly on the definition used. The authors found a higher prevalence in those studies which had used blood antigenemia as the test to detect a systemic infection, and in those which had used tissue PCR with a cut-off of 10 copies/mg tissue for diagnosing the CMV intestinal disease. In the same study the prevalence was also influenced by the geographical area and the sub-population considered. Higher prevalence was reported in those patients from East Asia, and in those with a diagnosis of steroid-refractory disease. Overall, the prevalence (both for systemic infection and intestinal disease), ranged from less than 5% to more than 35% in different studies. This big gap is the consequence of the different definitions of CMV infection adopted, but also the misleading definitions of the populations included in the studies (some studies have included CMV primary infections with CMV reactivations, patients with different stages of disease, and even patients with different diseases, like colon Crohn's disease and UC). Finally, there is a lack of inception-cohort studies and the data on which our knowledge relies are almost completely the result of referral cohorts, leading to a selection-bias risk.

Despite all these limitations, CMV infections (systemic or intestinal) are more common in patients with an active severe form. CMV has been found in a third of samples from patients

with severe UC [11], while the detection of CMV DNA should be considered rare in the mild/inactive forms [12]. Furthermore the prevalence is particularly high in patients with a steroid-refractory disease (above 30-40%) [13-15].

We conducted a study to evaluate the prevalence of CMV infection among patients with severe UC at their admission to our hospital. A proctoscopy and a biopsy together with blood sample CMV determination were obtained in all the patients admitted to our Internal Medicine Unit for severe colitis. In 9 of the 42 patients a CMV reactivation was diagnosed, 4 of them with a steroid-refractory disease [16]. Kambham et al., found a significant difference in the prevalence of colon CMV infection among patients with or without a steroid refractory disease (25% *vs* 2.5%) [17]. In the recent published study by Lee et al. [18], almost 150 patients with acute severe UC were retrospectively analyzed. The prevalence of CMV infection was 33.6%. The need for rescue therapy was 2.28-fold higher in the CMV+ group than in the CMV- group on multivariate analysis (95% confidence interval, 1.10-4.72). The authors also showed that recent use of high-dose steroids (odds ratio 3.30; 95% confidence interval, 1.33-8.19), and a higher Mayo score (odds ratio 1.58; 95% confidence interval, 1.05-2.38) were risk factors for CMV colitis. This link has been confirmed in another meta-analysis, designed to evaluate the relationship between CMV infection and steroid-refractory IBD, including 11 studies, with a total of 867 patients. A prevalence of 70% of steroid-resistance was found in the CMV positive groups compared with 34.5% in the CMV negative group (OR 2.12; 95% CI: 1.72-2.61). The link between steroid-resistance and CMV infection is considered so strong that the ECCO guidelines suggest testing only patients with acute steroid-refractory colitis, by tissue IHC or PCR [6].

Maconi et al., evaluated the characteristics of 77 UC patients who underwent colectomy (IHC was used to detect the presence of a CMV infection), and the authors noticed a higher prevalence of CMV in patients with steroid refractory UC, among those 77 patients 6 had a toxic megacolon (TM) [19]. It is not easy to find strong evidence on TM. A lot of case reports and small series are available, but there is a general lack of high quality, large-population prospective-studies, above all because of the rarity of the condition and its poor prognosis. We recently reported a series of 24 patients with TM who were admitted to our Unit between 1990 and 2011. The prevalence of CMV infection was 46% (11/24), while the percentage of steroid resistance was 45% (5/11) in patients with CMV, while it was 24% among the matched control group without CMV [20].

Another interesting aspect is the prevalence of CMV infection of the ileo-anal pouch. This is a hotly debated issue with a lack of high quality evidence to base our understanding on. Recently a retrospective analysis from the pathology database of the Mayo Clinic in Rochester has been published. The authors screened 2559 pouch biopsies, identifying CMV only in seven cases (0.0027%) [21]. This result is very interesting, because it could mean that CMV has a specific tropism for the colon mucosa, while its role on ileal tissue is modest, and it was also observed in Crohn's Disease, where the colon tissue is more frequently damaged by CMV than the ileum.

What is the real impact of CMV in the course of UC?

The role of CMV infection/reactivation in IBD is hotly debated. On one side there are clinicians who believe in a mere bystander role for the virus, but on the opposite side others sustain the thesis of a great involvement of the virus in the development of steroid resistance and the severe UC flare-ups, considering CMV a risk factor for medical treatment failures, toxic megacolon and emergency colectomy. Unfortunately, there is a lack of long-term studies on the course of CMV infection in patients with UC. Furthermore, the majority of studies have important limitations: retrospective analysis, small populations, lack of uniformity between detection methods and definition for CMV infection or reactivation, lack of established cut-offs for tissue and plasmatic quantification of CMV particles. This is why the studies are difficult to compare; it is impossible to draw definitive conclusions.

In one of the rare long-term studies available, Matsuoka et al. proved that periodic reactivation of CMV is possible in patients with UC and reactivation usually disappeared without any specific treatment [22]. The large majority of reactivation cases are self-limited and do not require any cessation of the IM. We have published a study on the natural history of CMV infection in patients with moderate-to-severe UC. In this study we considered the patient as a candidate for antiviral therapy only if both tests (histology and pp65 antigenemia) were positive. Among 85 tested patients 28 were CMV positive (above 33%), and 22 of them also had an endoscopic long-term FU: 19 of these 22 patients were in clinical remission on IM, and 8 of them remained positive for CMV viral DNA detection by PCR, after recovery from the colitis flare-up [23]. Delvincourt M. et al., evaluated the impact of CMV reactivation and its treatment on the course of IBD in a multi-center referral French IBD population [24]. In that case-control study the authors compared a population of UC patients during flare-ups with positive-blood CMV-PCR without antiviral treatment, to matched patients with negative-blood CMV-PCR. Secondly, in a retrospective study they compared the outcome of treated and untreated flare-up patients with CMV reactivation, diagnosed with PCR on blood or tissues. In the case-control study no differences were observed between the two groups in terms of length of stay and colectomy rate. Furthermore, no difference was observed in colectomy rate at 3 months, comparing treated and untreated patients with antiviral agents.

In any case, considering the short-term prognosis, in recent years a general consensus has been growing on the unfavorable effect of a CMV infection, or reactivation in UC. From the studies on prevalence, some of which have been discussed above, it is possible to observe a link between CVM infection and the resistance to steroids, the severity of the diseases, the risk of failure to IM, toxic megacolon, and the risk of surgery [25-31]. Currently, the exact direction of the causal relationship is difficult to assess and the hypothetical mechanism of this phenomenon is unknown, but in these studies it is possible to observe an unfavorable impact on a short-term outcome in patients with a CMV positive active UC, compared to non-viremic patients.

A dynamic correlation between the levels of CMV specific CD4 T cells and CMV viremia has been shown by Widmann et al., in an *in vitro* experiment [32]. The authors have also supposed a dose-dependent effect of steroids on the suppression of the CMV

specific T-lymphocyte function. On the other hand, an *in vitro* tropism of CMV for the inflammatory tissues in patients naive to steroids has been observed [33], suggesting a role for mucosal inflammation.

In a meta-analysis of individual patient data, the link between CMV infection and steroid resistance has also been evaluated and established in the immunocompetent host [34]. In a mean FU time of 13.4 months the authors were able to show a good prognosis without treatment in healthy young patients (<55 years old), while advanced age, male gender, presence of immune-modulating comorbidities, and need for surgical intervention were factors negatively influencing survival.

Predictors of CMV infection

Other predictors of CMV infection could be considered: a history of immunomudolators, except anti-TNF, age >30 years, steroid-refractory disease, presence of large endoscopic ulcers (Figure 1). Those aspects emerged in a retrospective case-control study by McCurdy et al. [35]. The density of viral components in biopsies should also be considered a predictor of unfavorable outcome and a marker of active CMV infections. Robin et al. have demonstrated that a viral load >250 copies/mg tissue is associated with an increased risk of failure in three successive lines of therapy [9].

Which patients need an antiviral treatment, and when should the immunomodulator be stopped?

Use of antiviral agents in patients with a severe reactivated UC is not a simple medical decision. Ganciclovir and Foscarnet are the most widely used drugs, even though there is no Randomized Control Trial (RCT) that has compared the efficacy of the two agents, and there is no strong evidence on the regimen to be adopted in an IBD setting. Furthermore, it should be stressed that both drugs have a lot of potentially serious side-effects, including bone marrow suppression, pulmonary and neurological dysfunctions, and renal toxicity. The benefit/risk ratio should be carefully evaluated before starting therapy under such extreme conditions. A great number of case reports have supported the positive impact of antiviral therapy in patients with severe UC, considering some clinically relevant outcomes such as the colectomy rate, length of hospitalization, clinical remission or mucosal healing. However, there are also some reports of patients who cleared the virus receiving immunosuppressors. In 2001 we conducted a retrospective study recording the prevalence of CMV on the course of IBD. In patients with severe steroid-refractory UC, antiviral treatment with ganciclovir or foscarnet was associated with a better outcome and clinical remission [14]. In contrast, in a French retrospective study patients with moderate-to-severe CMV-positive UC had a favorable outcome with IM alone [36]. Interestingly, in another retrospective observation, three of seven patients, admitted to our unit with severe UC responded to steroid or cyclosporine without any antiviral treatment, showing no benefit of antiviral treatments [16].

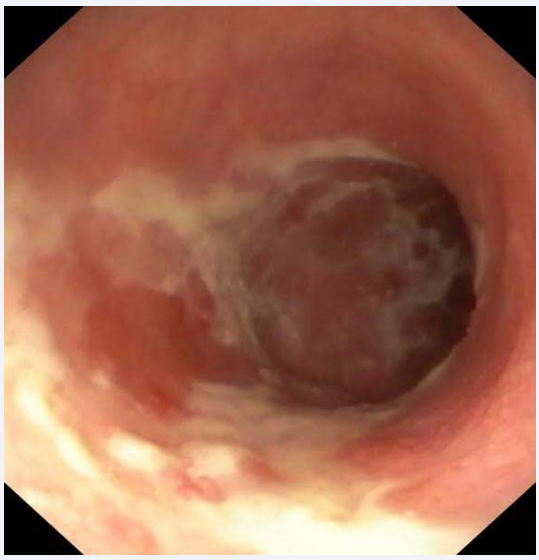

Figure 1 The presence of large endoscopic ulceration could be considered predictive of CMV infection. Performing the biopsies in the ulcerated mucosa increased the chances of finding CMV particles. The viral density is an important issue and has therapeutic consequences.

A meta-analysis recently published has evaluated the effectiveness of antiviral treatment in UC patients with a CMV active infection. Fifteen studies were included, considering over 300 patients (diagnosed by IHC and/or PCR on tissue), 43% treated and 57% untreated with antivirals. Interesting, considering the overall population there is no difference in terms of risk of colectomy, but restricting the analysis to steroid-refractory patients treated with antivirals patients were at lower risk of surgery (OR 0.2; 95% CI: 0.08-0.49) [37]. Probably, what is more important is the selection of patients to treat. The advantage of an antiviral therapy is more clearly seen in patients with a "high grade infection" (more than 250 CMV copies/mg tissue), than in those with a low grade infection, in which the benefit of antiviral treatment does not reach statistical significance [38,39].

Regarding immunomodulators, an increased risk of active CMV infection has been described in patients who had received cyclosporine [40], even though in our experience [16] we have seen remission and viral clearance in severe UC CMV positive patients treated with cyclosporin, without any antiviral agent.

Concerning anti-TNF agents, their use seems to be very safe and has not been associated with an increased risk of CMV reactivation [41]. We also reported 19 CMV positive patients who did not progress on their severe UC under immunosuppression in a long-term endoscopic FU [23]. A disappearance of CMV has been described after treatment of 2 refractory-UC patients treated with infliximab and one treated with leucapheresis. [42]. D'ovidio et al., evaluated the severity of CMV infection in IBD patients (4 of them with a severe UC), after a standard 3-infusion course of Infliximab. Conventional histology and immunohistochemical stains were negative for CMV in all the patients, without evidence of CMV disease after treatment, although in two of the eleven patients very low CMV-DNA levels were found in the colon biopsies after treatment, albeit with no evidence of worsening of the colon disease. The authors concluded that in their experience an active CMV infection does not progress to disease following Infliximab therapy [43]. The ECCO guidelines recommend antiviral treatment in CMV positive patients with severe steroid-resistant forms, receiving immunomodulators. There is an

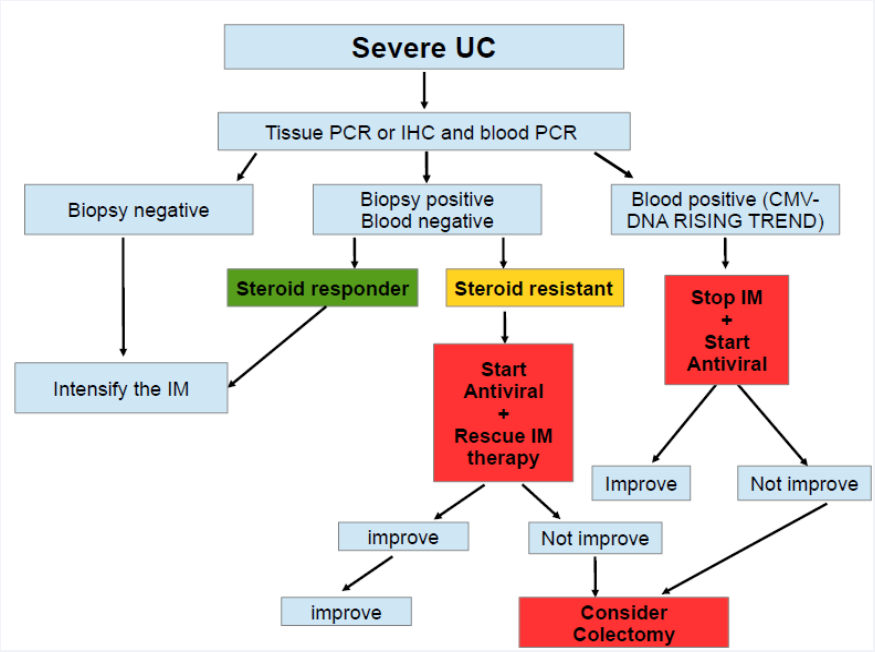

Figure 2 Therapeutic algorithm for severe flare-ups of ulcerative colitis in patients at risk of CMV active infection.

Table 1: Diagnostic tests for CMV infection.

CMV-infection	IgG	IgM	Tissue DNA (PCR)	Immunohistochemistry	Blood DNA (PCR)
Active	+	+/-	+	+	+
Inactive	+	-	+/-	+/-	+/-
Reactivation	+	+	+/-	+/-	+/-

indication to stop the immunomodulator therapy only if systemic infection is diagnosed. This evidence is supported by expert opinions or retrospective studies but no RCTs on this issue have been done so far.

The regimen suggested is ganciclovir as a first line and foscarnet as an alternative. The treatment should be prolonged for 2-3 weeks. It is recommended to switch to oral valganciclovir after 5 days ganciglovir iv, but some authors do not agree with this strategy because of the potential malabsorption of oral drugs during UC flare-ups.

An important issue is that there is no available threshold, on which to base a clinical decision making process. The cut-off of 250 copies/mg tissue suggested by Roblin et al. [9], should not be considered the main aspect on which to base a decision to start an antiviral agent or not, and to stop an IM, even though it was associated with an increased risk of treatment failure. The same aspects should be considered concerning blood quantification with real-time PCR. There is no validated viral-load cut-off to look at, when a positive blood-test reveals a CMV infection, but we consider a rising trend of viral load more useful. We believe that a step by step and personalized approach should be preferred and we have tried to simplify our clinical practice using a therapeutic algorithm (Figure 2).

CONCLUSIONS

The link between Cytomegalovirus infection and Inflammatory Bowel Diseases, particularly Ulcerative Colitis is well known, but the exact direction of this relationship is hotly debated by those clinicians who believe in a "bystander role" of the virus in a background of an inflammation, and those who postulate an important role of the virus in the development of steroid-resistance, severity of the disease, and some complications such as Toxic Megacolon. During recent decades a lot of definitions of "CMV infection" and a great number of methods to detect the virus in the blood and in the colon tissue have been proposed.

Immunohistochemistry (IHC), together with classic histological hematoxylin and heosin (HE) staining are considered valid methods, but real time PCR is the most widespread technique, probably because of its simplicity and rapidity and it is suggested as a diagnostic test by the ECCO guidelines, both in tissue and in blood, even though there is a lack of standardized methods, and no sure thresholds have been established. Generally, 10 CMV DNA copies/mg tissue (real time PCR), is considered quite sensitive and a CMV-DNA load above 250 copies/mg tissue has been associated with steroid resistance. In contrast, there is no officially approved cut-off for blood detection.

Overall, the prevalence (both for a systemic infection and for an intestinal disease) ranged from less than 5% to more than 35% in different studies. This big gap is the consequence of the different definitions of CMV infection adopted, the different populations included in the studies, and the different geographical areas.

There is a selection-bias risk in the great majority of the published papers because of the lack of inception-cohort studies. Despite all these limitations, CMV infections (systemic or intestinal) are more common in patients with an active severe form, rising to 30-40% among patients with a steroid-refractory disease, and over 40% in patients with Toxic Megacolon. In contrast, there is no correlation with ileo-anal pouch inflammation.

The role of CMV infection in UC, as well as in IBD generally, is hotly debated. There is evidence that has shown a significant association with steroid-refractory UC, severity of the disease, and some complications such as toxic megacolon, but there is a lack of studies on prognosis to evaluate the real long-term impact of CMV on severe UC. Even in some *in vitro* experiences contrary results have been produced. Whether CMV is an "innocent bystander" of the process of mucosal inflammation, with its particular tropism for the damaged colon tissue, is still an open question. However, it should be emphasized that there is a growing consensus on considering active CMV infection as a predictor of unfavorable outcome in patients with steroid-resistant UC, particularly in a short-term prognosis. Resistance to different lines of treatment, age >30 years, exposure to high dose steroids, presence of large mucosal ulcerations at the endoscopic examination, and high density colon infection are the main aspects to be considered.

There is no validated viral-load cut-off to look at, when a positive blood-test or positive histology reveal a systemic or a colon infection. We believe that a step by step and personalized approach should be preferred. As a general rule antiviral treatment should be adopted in CMV positive patients with severe steroid-resistant forms, receiving immunomodulators. IMs are generally safe and an ongoing treatment with anti-TNF has been administered to CMV positive UC patients without any effect on the course of the infection. There is an indication to stop the immunomodulator therapy only if systemic infection is diagnosed. The regimen suggested is ganciclovir as a first line and foscarnet as an alternative. The treatment should be for 2-3 weeks.

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Cite this article

Affronti A, Cottone M (2017) Cytomegalovirus in Ulcerative Colitis: Bystander or Leading . Clin Res Infect Dis 4(1): 1046.