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EDITORIAL

Cytomegalovirus and inflammatory bowel disease; reconsidering a 'result or reason dilemma' in terms of viral pathogenesis and medical ethics

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1. Introduction

Cytomegalovirus (CMV) is often detected in the inflamed colonic mucosa in patients diagnosed with inflammatory bowel disease (IBD). To date, it is an unresolved debate topic whether CMV is the cause of the inflammation in the intestinal mucosa or merely a bystander [1]. Available evidence predicts a worse prognosis for IBD patients diagnosed with a CMV infection [2,3]. CMV-infected patients have a higher risk of steroid-refractory [4]. Therefore, the European Crohn's and Colitis Organization (ECCO) guidance recommended reserving CMV screening in colonic biopsy materials for steroid-refractory (SR) patients [5]. On the other hand, the British Society of Gastroenterology guideline strongly recommends screening all biopsy materials for CMV [6]. Both guidelines recommend administering ganciclovir to CMV-positive IBD patients.

2. The dilemma

The debate is still on to decide whether CMV infection is the cause or rather a consequence of the inflammation in the intestinal mucosa [7]. If CMV causes inflammation, anti-viral suppression should prove an efficient treatment. Unfortunately, current evidence is not supporting this view. A recent meta-analysis failed to provide evidence of the beneficial effect of antiviral suppression on the adverse outcomes among ulcerative-colitis (UC) patients [8]. In this study, we present a meta-analysis, based on the combined data from 191 ganciclovir-treated and 166 non-treated UC patients diagnosed with a CMV infection. The association of ganciclovir treatment with primary outcomes (colectomy or death) was assessed using both frequentist and Bayesian approaches. The combined effect estimates in this meta-analysis did not encourage ganciclovir administration to CMV-infected UC patients. The Bayesian random-effects model, on the other hand, suggested that future studies will probably encourage ganciclovir treatments neither.

Moreover, previous research demonstrated that among steroid responders CMV disappears from the colonic tissue in the absence of antiviral suppression [9]. CMV is reportedly activated and deactivated without antiviral suppression in IBD patients [10]. Therefore, deciding the question 'whether CMV infection is the cause or rather a consequence of the inflammation' is of utmost interest.

3. CMV & viral pathogenesis

CMV is a double-stranded DNA virus that is highly prevalent among humans and mostly acquired in childhood. Seroepidemiologic studies have demonstrated a 90% CMV prevalence in certain geographic regions [11,12]. CMV persists in a latent form over the entire lifetime of the host in specific myeloid progenitor cells that undergo reprogramming from hematopoietic stem cells [13]. When remote stimuli induce the differentiation of CMV-infected latent myeloid cells toward mature dendritic cells (DCs) and/or macrophages, CMV reactivation and transcription are simultaneously triggered as well [14]. Therefore, CMV is reactivated multiple times during the life of seropositive patients. A previous study describes 83% viruria and 52% viremia among healthy individuals, during a median duration of 30 months follow up [15]. In the same study, none of the subjects were presented with a disease state. It is important to keep in mind that CMV takes part in the common evolution in both primate and human holobionts for millions of years [16]. Therefore, CMV detection does not necessarily indicate a clinically relevant, symptomatic infection.

The colon is the most frequently reported CMV infection site, especially in IBD and AIDS patients. CMV infection- or reactivation-associated flare-up from latency is an unresolved problem in CMV pathogenesis. In a recent study, researchers emphasize the presence of the IE antigen, which is mainly assumed to indicate CMV replication in the rectosigmoid epithelial cells of HIV/CMV co-infected patients [17]. In addition, the researchers have developed an *in vivo* modeling by inoculating human intestinal epithelial cells subcutaneously in immune deficient mice to better understand CMV pathogenesis. Their experiments concluded in a statistical difference between the CMV-inoculated cells compared to mock-inoculated cells concerning IE expression, proinflammatory cytokine release, intestinal epithelial cell disintegration, increased epithelial cell permeability and the other pathological changes.

We believe that this valuable work raised several important aspects that are worth discussing. On the one hand, target cell tropism is a required step for viral pathogenesis, which is

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Article highlights

- CMV takes part in the common evolution both in primate and human holobionts for millions of years
- Cytomegalovirus (CMV) is often detected in the inflamed colonic mucosa of patients diagnosed with inflammatory bowel disease (IBD)
- The debate is still on to decide whether CMV infection is the cause or rather a consequence of the inflammation in the intestinal mucosa
- There is no study showing that colonic mucosal epithelial cells would be permissive for CMV entry and replication
- CMV-bearing phagocytes, recruited to the inflammation site might encounter the outcome, either in a positive or in a negative way
- Ganciclovir has an unacceptable adverse effect-rate
- Well-designed comparative studies are needed for treatment advice

mediated through specific receptors [18]. In addition, Platelet-derived growth factor receptor alpha (PDGFRα) has been identified as an entry receptor for CMV on monocytes and fibroblasts [19]. Several additional receptors and binding proteins, such as CD46, THY-1 cell surface antigen (CD90), heparin sulfate proteoglycans (HSPGs), integrins, epidermal growth factor receptor (EGFR), CD147, OR14I1, and recently neuropilin-2 (Nrp2) have been studied for exploring the CMV entry mechanisms in other cell types [20]. Whether these proteins function as real receptors or post-entry steps remains elusive. On the other hand, early antigen detection in a cell line cannot be considered as direct proof of infection. For instance, *in vitro* cell culture studies with SV40 and Murine polyomavirus (MPyV) showed that permissive cells expressed viral genes and underwent cytolysis, while non-permissive cells did not allow the development of new virions, only expressed some early antigens [21] Therefore, the detection of early antigens in a cell line is not a direct proof of a productive or a permissive infection.

Taken together, viruses are highly selective for their target cells; a cell line is either 'permissive or not'. Therefore, a vast majority of humans experience CMV viremia without developing an inflammatory bowel disease (IBD) during their life [15]. However, it is possible that CMV is more than an innocent bystander, present in the colonic mucosa. Human CMV encodes for several cytokine-homolog proteins [22]. These homolog proteins might fulfill certain immunomodulatory roles. Thus, CMV-bearing phagocytes recruited to the inflammation site might encounter the outcome, either in a positive or a negative way [23–25].

4. Ganciclovir & medical ethics

4.1. Ganciclovir

Ganciclovir is a nucleoside-analog, acting as a suppressor for CMV DNA polymerase replication activity, and to a lesser extent for other herpes virus polymerases [26]. Ganciclovir requires phosphorylation by viral and/or cellular kinases before being incorporated and eventually performing its DNA replication inhibitory activity. Formerly it was presumed that Ganciclovir is solely activated in CMV-replicating cells and is highly specific to CMV polymerase. However, subsequent experience demonstrated that ganciclovir is a highly toxic substance and might be far less selective than previously thought [27]. A recent therapeutic drug monitoring study followed 82 patients, receiving ganciclovir [28]. This study described that 96.3% of the patients experienced leukopenia, while 79.3%, 81.7%, and 54.9% experienced thrombocytopenia, anemia, and neutropenia, respectively. Beyond that, the side effects were not associated with concentrations of ganciclovir. However, the study also reported about the side effects of ganciclovir among transplant patients and therefore, should be also evaluated in this context. To our recent knowledge, ganciclovir toxicity has not yet been reported in UC patients.

4.2. Medical ethics

Autonomy, beneficence, non-maleficence, and justice are the core principles of medical bioethics [29]. Although none of these principles has superiority over the others, we would mention the beneficence and non-maleficence as examples in this text. The principle 'beneficence' is valid along with 'non-maleficence', as well as with the other two previous principles. Thus, maintaining a strict balance between beneficence and non-maleficence is fundamental. The evidence derived from research is the pathfinder for maintaining the balance between benefit and harm. Evidence-based medical practice induces an evolution of normative medical ethics toward evidence-based ethics [30]. In evidence-based medicine, randomized-controlled studies and meta-analysis occupy the highest degrees of the evidence hierarchy, followed by cohort- and case-control studies. Therefore, current evidence must refer to a well-applied meta-analysis, whenever available. A recent meta-analysis failed to show a promising effect of ganciclovir administration among ulcerative colitis patients [8]. Therefore, it would not be wrong to state that current evidence does not support the ganciclovir administration to ulcerative colitis patients.

5. Conclusion

Whilst CMV does not cause intestinal inflammation in people, especially in neonatal and early childhood periods, can it be a trigger for a lytic infection under different conditions? As aforementioned, the possibility of a positive answer to this question contradicts our basic knowledge on viral pathogenesis. However, it may be a more rational approach to try to understand what stimulus that activates both CMV and dendritic cells (DCs) and/or macrophages together. The fact that we do not know exactly what we are treating should be considered an adequate reason to not intervene, especially with a highly toxic substance.

6. Expert opinion

We believe medical ethics would dictate to delay CMV suppression as an optional IBD management approach until the publication supporting data resulting from well-designed comparative studies.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Cottone M, Pietrosi G, Martorana G, et al. Prevalence of cytomegalovirus infection in severe refractory ulcerative and Crohn's colitis. Am J Gastroenterol. 2001;96(3):773–775.
2. Lv Y-L, Han -F-F, Jia Y-J, et al. Is cytomegalovirus infection related to inflammatory bowel disease, especially steroid-resistant inflammatory bowel disease? A meta-analysis. Infect Drug Resist. 2017;10:511–519.
3. Wu X, Wu L, Ji H, et al. Relationship between cytomegalovirus infection and steroid resistance in inflammatory bowel disease: a meta-analysis. Dig Dis Sci. 2015;60(11):3203–3208. .
4. Maconi G, Colombo E, Zerbi P, et al. Prevalence, detection rate and outcome of cytomegalovirus infection in ulcerative colitis patients requiring colonic resection. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2005;37:418–423.
5. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019;13:144–164.
6. Lamb CA, Kennedy NA, Raine T, et al. British society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68:gutjnl-2019-318484.

• **British Society of Gastroenterology guideline strongly recommends CMV screening in all intestinal biopsy specimens of inflammatory bowel disease patients. In CMV positive patients guideline also strongly recommends ganciclovir treatment although weak evidentiary.**

7. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? Inflamm Bowel Dis. 2010;16(9):1620–1627.
8. Yilmaz Karadag F, Arslan F, Caskurlu H. et al., Efficacy of antiviral treatment in cytomegalovirus detected ulcerative colitis: meta-analysis of available data. Scand J Gastroenterol. 54(11):1346–1352. 2019.

•• **The Bayesian random-effects model generated meta-analysis revealed that future studies will favor non-treatment of ulcerative colitis with ganciclovir.**

9. Kim YS, Kim Y-H, Kim JS, et al. The prevalence and efficacy of ganciclovir on steroid-refractory ulcerative colitis with cytomegalovirus infection: a prospective multicenter study. J Clin Gastroenterol. 2012;46(1):51–56.
10. Matsuoka K, Iwao Y, Mori T, et al. Cytomegalovirus is frequently reactivated and disappears without antiviral agents in ulcerative colitis patients. Am J Gastroenterol. 2007;102(2):331–337.
11. Kothari A, Ramachandran VG, Gupta P, et al. Seroprevalence of cytomegalovirus among voluntary blood donors in Delhi, India. J Health Popul Nutr. 2002;20(4):348–351.
12. Yeshwondm M, Balkachew N, Delayehu B, et al. Seroepidemiology study of cytomegalovirus and rubella among pregnant women at St. Paul's hospital millennium medical college, Addis Ababa, Ethiopia. Ethiop J Health Sci. 2016;26(5):427–438.
13. Zhu D, Pan C, Sheng J, et al. Human cytomegalovirus reprogrammes haematopoietic progenitor cells into immunosuppressive monocytes to achieve latency. Nat Microbiol. 2018;3(4):503–513.
14. Reddehase MJ, Lemmermann NAW. Cellular reservoirs of latent cytomegaloviruses. Med Microbiol Immunol (Berl.). 2019;208(3–4):391–403.
15. Arora N, Novak Z, Fowler KB, et al. Cytomegalovirus viruria and DNAemia in healthy seropositive women. J Infect Dis. 2010;202(12):1800–1803.
16. Murthy S, O'Brien K, Agbor A, et al. Cytomegalovirus distribution and evolution in hominines. Virus Evol. 2019;5(2):vez015.
17. Maidji E, Somsouk M, Rivera JM. et al., Replication of CMV in the gut of HIV-infected individuals and epithelial barrier dysfunction. PLoS Pathog. 13(2):e1006202. 2017.

•• **The authors claimed that CMV is the leading factor in HIV related intestinal mucosal inflammation with disrupting epithelial junctions.They showed CMV IE proteins, as a surrogate marker for CMV replication in the nuclei of intestinal epithelial cells of the some HIV/CMV coinfected patients.**

18. Payne S. Viruses: from understanding to investigation. USA: Academic Press; 2017.
19. Wu K, Oberstein A, Wang W, et al. Role of PDGF receptor-α during human cytomegalovirus entry into fibroblasts. Proc Natl Acad Sci U S A. 2018;115(42):E9889–E9898. .
20. Stein KR, Gardner TJ, Hernandez RE. et al., CD46 facilitates entry and dissemination of human cytomegalovirus. Nat Commun. [Internet]. 2019 cited 2020 Feb 19; 10(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6586906/.
21. Nathanson N. Viral pathogenesis and immunity. USA: Elsevier; 2007.
22. McSharry BP, Avdic S, Slobedman B. Human cytomegalovirus encoded homologs of cytokines, chemokines and their receptors: roles in immunomodulation. Viruses. 2012;4(11):2448–2470.
23. Smithey MJ, Venturi V, Davenport MP. et al., Lifelong CMV infection improves immune defense in old mice by broadening the mobilized TCR repertoire against third-party infection. Proc Natl Acad Sci U S A. 115(29):E6817–E6825. 2018.

• **The authors described CMV seropositive mice have a robust immune defense to the Listeria monocytogenes infection than seronegative ones. They have drawn attention to the probable positive effect of CMV on human immunity in terms of the co-evolutionary.**

24. Wilski NA, Del Casale C, Purwin TJ, et al. Murine cytomegalovirus infection of melanoma lesions delays tumor growth by recruiting and repolarizing monocytic phagocytes in the tumor. J Virol. 2019;93:e00533–19.
25. Dennis EA, Smythies LE, Grabski R, et al. Cytomegalovirus promotes intestinal macrophage-mediated mucosal inflammation through induction of Smad7. Mucosal Immunol. 2018;11(6):1694–1704.
26. Faulds D, Heel RC. Ganciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. Drugs. 1990;39(4):597–638.
27. Millar AB, Miller RF, Patou G, et al. Treatment of cytomegalovirus retinitis with zidovudine and ganciclovir in patients with AIDS: outcome and toxicity. Genitourin Med. 1990;66(3):156–158.
28. Ritchie BM, Barreto JN, Barreto EF, et al. Relationship of ganciclovir therapeutic drug monitoring with clinical efficacy and patient safety. Antimicrob Agents Chemother. 2019;63:e01855–18.
29. Gillon R. Medical ethics: four principles plus attention to scope. BMJ. 1994;309(6948):184–188.
30. Goldenberg MJ. Evidence-based ethics? On evidence-based practice and the "empirical turn" from normative bioethics. BMC Med Ethics. 2005;6(1):E11.

•• **Authors emphasize the importance of bioethics term that may be threatened by the evidence-based ethics in the modern medicine era.**