

# Risk of cytomegalovirus reactivation in patients with immune-mediated inflammatory diseases undergoing biologic treatment: a real matter?

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## SUMMARY

The use of biological agents has grown exponentially in immune-mediated inflammatory diseases (IMID), often achieving a good control of disease progression and improving patients' quality of life. However, their use resulted in an increased risk of adverse events, including reactivation of chronic/latent infectious diseases. As for the risk of Cytomegalovirus (CMV) reactivation, very few data are available. We reviewed the literature reporting cases of CMV infection in IMID patients during biological therapy. Although the risk of CMV reactivation cannot be excluded, we concluded that there is no evidence to warrant CMV screening before starting a biological agent.

**Key words:** Cytomegalovirus; screening; biological agents; inflammatory diseases

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## ■ INTRODUCTION

In rheumatic diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) and in other immune-mediated inflammatory diseases (IMID), such as chronic inflammatory bowel diseases (IBD) or multiple sclerosis (MS), biological treatments have been largely employed.

Their use has resulted in an increased risk of new infectious events and reactivation of chronic/latent infectious diseases. In other immunosuppression conditions (solid organ transplant, Acquired Immune Deficiency Syndrome- AIDS), the risk of viral infections reactivation is well known. This problem seems to be less evident in IMID patients who assume anti-tumour necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) or other biologic therapies, although reactivations of Varicella-Zoster virus (VZV) and John Cunningham virus (JC) have been widely reported. As for CMV reactivation, very few data are available in patients with IMID un-

dergoing biological treatment. Before starting biological therapy the screening for CMV infection is not recommended in the evidence-based consensus by the European Crohn's and Colitis Organization (1), by the European League Against Rheumatism (EULAR) (2) and by the Italian Society for Rheumatology (3).

The aim of this work is to update the literature evidence on the risk of CMV reactivation in IMID patients, in order to understand if screening before biologic therapy is necessary.

## ■ MATERIALS AND METHODS

A review of Pubmed and indexed literature on CMV and IMID was carried out. The following search terms were used in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>): Cytomegalovirus, anti-TNF, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel diseases. We included case report or case series until April 2015.

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## ■ RESULTS

In the 3-year prospective French RATIO registry, including 57,711 patient/year undergoing biologic therapy for a broad spectrum of IMID, Salmon-Ceron et al. (4) described 3 disseminated CMV infections in Crohn's disease.

It is not clear if the cases were primary infections or reactivations, but one patient was HIV (human immunodeficiency virus) positive and had a *Pneumocystis pneumonia*. During immunomodulating therapy for IBD, severe CMV reactivations are rarely reported and only in one case with poor outcome (5).

In the other case reports, the antiviral treat-

ment and the discontinuation of the immunosuppressive agents were associated with clinical improvement (6-9). The role of CMV in the exacerbations of IBD remains a topic of ongoing debate. CMV colitis is rare in patients with Crohn's disease or mild to moderate ulcerative colitis, but CMV reactivation can be detected in about 30% of patients with severe and/or steroid-refractory ulcerative colitis, with remission rates of 67-100% following antiviral therapy with intravenous ganciclovir. However, despite an inconclusive knowledge, testing for CMV reactivation should be performed in presence of refractory colitis and, in case of a positive result, antiviral therapy should be started (10).

**Table 1** - CMV infections occurred during biological therapy in IMID patients.

Author	Year	IMID	Treatment at the time of CMV infection	Primary infection (P) or reactivation (R)	Trattamento	Esito
Salmon Ceron D et al. (4)	2011	3 Crohn's disease	Infliximab	NR	NR	Improvement 1 lost at follow up
Salmon Ceron D et al. (4)	2011	RA	Infliximab	NR	NR	Improvement
Pickering O et al. (5)	2009	Crohn's disease and sickle cell anemia	Infliximab 6-mercaptopurine	(IgG e IgM pos)	Ganciclovir DIT	Death
Charles et al. (6)	2010	Ulcerative colitis	Adalimumab Azathioprine Prednisone	R	Ganciclovir DIT	Surgery (colectomy)
Mizuta M et al. (7)	2005	Crohn's disease	Infliximab prednisone 6-mercaptopurine	(IgG e IgM pos)	Ganciclovir	Improvement
Kohara MM et al. (8)	2006	Crohn's disease	Infliximab 6-mercaptopurine	(IgG e IgM pos)	Ganciclovir, splenectomy	Improvement
Helbling D et al. (9)	2002	Crohn's disease	Infliximab Azathioprine Corticosteroids	P	Foscarnet/ Ganciclovir DIT	Improvement
Haerter G et al. (11)	2004	RA	Infliximab Cyclophosphamide Azathioprine	R	Ganciclovir/ valganciclovir	Initial relapse, then improvement
Petersen B et al. (12)	2008	PsA	Etanercept	P	DIT	Improvement
Petersen B et al. (12)	2008	PsA	Efalizumab	NR	DIT	Improvement
Vallet H et al. (14)	2011	RA	Rituximab	NR	Ganciclovir/ Valganciclovir IVIg	Improvement
Sari I et al. (15)	2008	Behcet's disease	Infliximab	R	Ganciclovir DIT	Improvement

IMID, immune-mediated inflammatory diseases; RA, rheumatoid arthritis; PsA, psoriatic arthritis; NR, not reported; DIT, discontinuation of immunomodulating therapy; IVIG, intravenous immunoglobulin.

Note: Reference 13 not included in the table due to the absence of available data on treatment and outcome.

Referring to the rheumatic diseases patients, the French RATIO registry reported one case with rash and fever due to CMV in RA (primary infection or reactivation?) (4). In other reported cases (11-15), the discontinuation of immunomodulating therapy led to the improvement of the patients' conditions, with or without concomitant antiviral therapy.

Haerter et al. (11) described a case of retinitis in a patient with RA with an impaired cellular immune state, probably due to treatment with cyclophosphamide and azathioprine. We found one report describing two CMV infections in patients affected by psoriasis during anti-TNF- $\alpha$  therapy (12). In case of the novel therapies for RA, like Janus Kinase (JAK) inhibitors (tofacitinib), an analysis to determine the rate of infections reported 6 cases of CMV infection, but it's not clear if the clinical presentation was severe neither if it was a primary infection or a reactivation (13). In Table I, we summarize the cases of CMV infection reported during biological therapy in IMID patients.

## DISCUSSION AND CONCLUSIONS

Our brief literature review is consistent with the hypothesis that, during anti-TNF- $\alpha$  therapy in IMID patients, CMV reactivation is possible, although the risk is very low.

The clinical reports did not describe clearly if infection was primary or a reactivation. As a result, we cannot recommend anti-CMV antibodies detection or CMV-DNA testing in the infectious diseases screening applied to patients before starting biological treatment. This recommendation is also supported by the fact that the pre-emptive therapy would be generally not indicated, with the exception of some groups of immunocompromised patients (hematopoietic stem cell transplantation or acquired immunodeficiency syndrome).

On the other hand, it is important to underline that, in patients receiving biological drugs, presenting fever of unknown origin, particularly if associated with rash, hepati-

tis or visual field defects, clinicians should be aware of the risk of CMV reactivation and specific diagnostic tools should be performed.

**Conflict of interest.** none

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