LATENT CYTOMEGALOVIRUS AND TOXOPLASMA INFECTIONS IN PATIENTS WITH RHEUMATIC INFLAMMATORY DISEASES TREATED WITH BIOLOGICAL AGENTS. PRELIMINARY RESULTS

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Objectives

The prognosis of patients with inflammatory joint diseases has greatly improved in the last few years, thanks mainly to the introduction of biological therapies. However, several lines of evidences suggest that long-term treatment with biological agents has an effect on susceptibility to opportunistic infections including those related to virus, bacteria, parasites and fungi, in patients with chronic inflammatory diseases.

Methods

We retrospectively analyzed peripheral blood mononuclear cell (PBMC) specimens from 50 patients of which 36 (72%) females, with a mean age of 53.2±2.2 years (range 29-78 years), enrolled at the Unit of Rheumatology of our University, from February 2009 to March 2014 for rheumatic inflammatory diseases (*i.e.*, rheumatoid arthritis (ReA), psoriatic arthritis (PA), ankylosing spondylitis (AS), diagnosed on the basis of the local clinical expert's opinion and receiving anti-TNF-a drugs (Infliximab, Adalimumab, Rituximab, Etanercept, Abatacept) from at least 5 years. Most patients had a serology for tuberculosis (Quantiferon TB-Gold, B and C hepatitis and HIV) but only few patients had a serology for Cytomegalovirus (CMV) and Toxoplasma gondii (Tg). After informed consent had been obtained from each patient and approval from the Institutional Local Ethic Committee, samples were tested at Section of Infectious Diseases by a qualitative in-house nested-PCR (n-PCR) for CMV, Tg, Pneumocystis jiroveci, according previous described methods. Primer pairs targeting B1 gene or Mag1 gene encoding for the 65 kDa cyst-surface antigen, were employed for T. gondii PCR.

Results

A total of seven (14%) out 50 patients consisting of 3 males and 4 females, mean age 55.1 years (range 44-71 years) (median duration of TNF-a antagonist treatment at onset of infection was 45.5 weeks (range, 16-73 weeks), gave PCR positive results.

Of these (Table 1), under infliximab treatment since 5 years, 4 had ReA, 3 AS. Six (12%) and 1 (2%) of them did detect CMV DNA or *T. gondii* DNA (Mag1), respectively and had a positive serology for both CMV and *T. gondii*. These patients, asymptomatic for CMV or T. gondii infection except for periodic fever, had suffered from other severe concomitant comorbidities and had previously treated with other immunosuppressive drugs (DMARDs). No specimen was positive for *Pneumocystis jiroveci*.

Discussion

Treatment with biological drugs is associated with increased susceptibility to viral infections. Although descriptions of CMV reactivation in course of anti-TNF-a are very rare (bibliographical search carried out on Medline via Pubmed and Embase (2008–September 2014) to investigate the occurrence of viral opportunistic infections, physicians should pay attention to the possibility of CMV infection during treatment with infliximab regimens especially in presence of unexplained fever. Infliximab might facilitate reactivation of some latent viruses such as CMV as it can block TNF-α, interfere with the recruitment of lymphocytes, and decrease interferon-γ levels, which are involved in control of the antiviral state. CMV complicating biological Immunosuppressive therapy has also been observed in two Patients with psoriasis receiving treatment with Etanercept or Efalizumab (3). These did not show asymptomatic infections, but were severely and prolonged fatigued.

Table 1. Clinic and Laboratory Characteristics of Rheumatologic Patients Under anti-TNF-Inhibitors With Latent Opportunistic Infections Detected by PCR.

Patient	Age/sex	Rheumatologic disease	Genetic trait	Biological drug	DMARDs	Comorbidities	Serology	Molecular Positivity (PCR)	Symptoms associated at time of PCR
FM	58/M	Ankylosing spondylitis	HLA-B27	Infliximab	MTX	Cutaneous Psoriasis	Positive CMV serology	CMV-DNA	None
GL	54/F	Rheumatoid arthritis	HLA-B27	Infliximab	MTX and Steroid	Cervical cancer	Positive CMV serology	CMV-DNA	None
PM	44/M	Ankylosing spondylitis	HLA-B27	Rituximab	MTX and Steroid	Crohn's disease since 2007 Basosquamous carcinoma of neck	Not available	CMV-DNA	Fever since four months
FO	71/F	Rheumatoid arthritis (low responder to therapy)	HLA-B27	Infliximab	Steroid Chloroquine	Interstitial lung disease	Positive Toxoplasma serology	T. gondii DNA Mag-1	Fever since 3 months
AA	44/M	Ankylosing spondylitis	HLA-B27	Etanercept	Steroid	None		CMV-DNA	None
SS	45/F	Rheumatoid arthritis	Not determined	Infiximab	MTX and Steroid	None	Positive CMV serology	CMV-DNA	Not available
CS	66/F	Ankylosing spondylitis	HLA-B27	Infiximab	MTX and Steroid	None	Not done	CMV-DNA	Negative

MTX= Methotrexate; DMARDs = Disease-Modifying Antirheumatic drugs

The only patient with the reactivation of T. gondii infection following infliximab administration which is known to interfere with host defense against toxoplasmosis, has been revealed by MAG1 DNA (212 bp fragment) detection. MAG-1 gene is a specific marker of bradyzoite stage which could have predictive value in toxoplasmic reactivation (1-2). This is the first study showing the presence of circulating DNA parasite following anti-TNF administration. A strict follow-up of this patient is in progress.

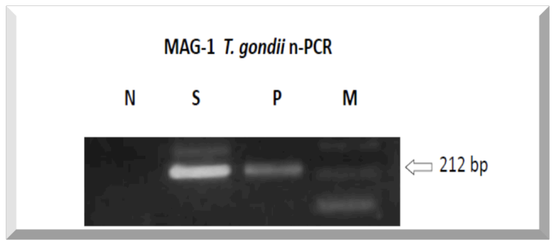

Figure 1: PCR T. gondii DNA. N: Negative control; S: CSF sample: P: Positive control, DNA extracted from RH strain; M: Marker (100 bp).

References

1.Contini C, Seraceni S, Cultrera et al. Evaluation of a Real-time PCR-based assay using the lightcycler system for detection of Toxoplasma gondii bradyzoite genes in blood specimens from patients with toxoplasmic retinochoroiditis. Int J Parasitol. 2005 Mar; 35(3): 275-83.

2. Contini et al. Clinical and diagnostic management of toxoplasmosis in the immunocompromised patient. Parassitologia. 2008; 50(1-2):45-50.

3. Petersen B, Lorentzen H. Cytomegalovirus complicating biological immunosuppressive therapy in two patients with psoriasis receiving treatment with etanercept or efalizumab. Acta Derm Venereol. 2008;88(5):523-4.