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Herpes virus, human papilloma virus and polyomavirus infection in patients undergoing biological therapy

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ABSTRACT

Biological therapy has redesigned the treatment of certain systemic inflammatory disorders, and it is currently employed in clinical practice by specialties such as rheumatology, dermatology, gastroenterology, neurology and oncology.

A decade's worth of data has classified biological therapy as safe and effective for the treatment of a large number of diseases. However, its associated risk of secondary infections remains a major issue, particularly when discussing long-term immunosuppressive treatment. Secondary viral infections can require delaying or discontinuing biological therapy, thus leading to a relapse or reactivation of the underlying disorder, and this can happen in patients with already limited therapeutic options.

Thorough screening and timely diagnosis of viral reactivations are necessary in order to maximize the benefits and reduce the risks associated with biological therapy. Viruses frequently associated with such reactivations include hepatitis B and C viruses, cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus. This review focuses on the risk of reactivation associated with biological therapy in patients with autoimmune diseases and underlying herpes virus, human papilloma virus and polyomavirus infections.

Keywords: biological therapy, viral infections, herpes virus, human papilloma virus, polyomavirus

BACKGROUND

Biological therapy has become the cornerstone for the treatment of many autoimmune conditions and malignancies. Biologics are immunomodulator agents (antibodies or other peptides) that interfere with the regular humoral immune response. Thus, in addition to beneficial effects in relation with the underlying disease, biological therapy also leaves the patient more susceptible to infection by inducing a certain degree of immunosuppression.

Well-known complications of this type of therapy include increased rates of bacterial and mycobacterial infections (1), as well as opportunistic infections with *Pneumocystis jiroveci* (2) or fungi (3,4). However, there is less standardized information available to describe the potential risk associated with reactivation of pathogenic viruses that remain latent in the host following primary infection. Reactivation occurs through a switch from latency to lytic replication (5), a process that may be triggered by various stimuli, including immunosuppression associated with biological therapy. The viruses frequently incriminated in reactivation under biological therapy include hepatitis B (6) or C (7) viruses, cytomegalovirus, varicella-zoster virus and Epstein-Barr virus.

This review focuses on the risk of reactivation associated with biological therapy in patients with autoimmune diseases and underlying herpes virus, human papilloma virus and polyomavirus infections.

Herpes simplex virus

Herpes simplex viruses (HSV) are part of the *Alphaherpesvirinae* subfamily. A correct diagnosis of HSV infection requires a polymerase chain reaction

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(PCR) on tissue or bodily fluid samples (8). HSV-1 and HSV-2 have the capacity to establish latency in sensitive neurons (9), such as the dorsal root ganglia, or trigeminal ganglia (10,11). HSV-1 latency has also been described in corneal tissue, its reactivation leading to herpetic keratitis (10), or in sympathetic thoracic ganglia (12).

The reactivation of herpes simplex viruses has been correlated with the use of rituximab, mainly in oncologic patients (13). Cornely et al. (14) have reviewed 992 patients receiving alemtuzumab, rituximab or both, and have identified a total of 299 (30.1%) opportunistic infections; of these, 30 (10%) cases represented HSV reactivations.

The field literature also reports isolated cases of herpetic encephalitis after therapy with anti-tumor necrosis factor (TNF)-α agents (15,16), and Justice et al. (17) have described a case of disseminated cutaneous HSV-1 infection in a patient with rheumatoid arthritis (RA) undergoing therapy with infliximab.

Acyclovir, valacyclovir or famciclovir can be used to treat acute or recurrent infection. The use of anti-TNF agents is not recommended during acute infection, due to an increase in the risk of dissemination (18). In patients with severe HSV infection, immunosuppressive therapy needs to be discontinued (19).

Varicella-zoster virus

Varicella-zoster virus is associated with two distinct clinical outlines: varicella (chickenpox) and herpes zoster (HZ, otherwise known as shingles). Varicella is the primary infection with VZV that commonly displays a benign, self-limiting evolution, particularly in childhood (20). The reactivation of the latent virus leads to herpes zoster and generally occurs during immune-depression (21,22), presenting as unilateral blistering rash, with dermatomal distribution, and often leading to complications such as chronic pain or post herpetic neuralgia (23).

VZV establishes latency reservoirs in dorsal root spinal ganglia and in cranial nerve ganglia (24). The latent virus has also been identified in the autonomic nervous system (25), particularly in sympathetic thoracic ganglia (12), or in neurons of the enteric nervous system (24).

In patients receiving treatment with anti-TNF-α agents, herpes zoster can present an atypical clinical picture, either disseminated (26) or mimicking other infections (27); a multi-dermatomal outline with multiple recurrences has also been described (28). Moreover, VZV reactivation has also been associated with encephalitis (29) or vasculopathy (30), with unfavorable and potentially fatal evolution.

Recent studies have shown that the risk of HZ significantly increases with old age, treatment with corticosteroids and a combination of anti-TNF-α and conventional disease-modifying antirheumatic drugs (c-DMARDs) (31). The incidence of HZ in patients undergoing treatment with anti-TNF-α is three-fold higher compared to the general population (32), the lowest risk being associated with adalimumab, and the highest one, with infliximab, according to the study performed by Galloway et al. (33) on the British Society for Rheumatology Biologics Register (BSRBR) cohort. Cases of HZ associated with tocilizumab (34-36) or rituximab (37) have also been reported.

The live attenuated shingles vaccine is recommended for prophylaxis of HZ in immunocompetent patients over 60 years of age (38). Published studies have reported a reduction in the risk of HZ with up to 70% in immunocompetent persons over 50 years of age (39). Despite of the fact that the HZ risk is 1.5 to 2 times higher in patients with immune-mediated diseases such as RA or Crohn's disease (40,41), the US Food and Drug Administration (FDA), the Advisory Committee on Immunization Practices (ACIP) and the American College of Rheumatology (ACR) do not recommend the administration of the shingles vaccine during treatment with biologics (42) due to safety issues, namely the risk of acute post-vaccination VZV infection. The vaccine can, however, be administered in these patients with a minimum of 3 weeks prior to initiating biological therapy, this timespan representing the incubation period for VZV.

A retrospective cohort study of 463,541 patients with ages above 60 years, with RA, psoriasis, psoriatic arthritis, ankylosing spondylitis or inflammatory bowel disease and enrolled in the Medicare social insurance system, has reported that the administration of the shingles vaccine was not associated with an increase in the incidence of herpes zoster immediately post-vaccination in patients undergoing treatment with biologics; furthermore, vaccination lead to a significant long term reduction in the risk of HZ in these patients (38).

In acute VZV infection biological therapy needs to be discontinued until all vesicles have cleared out,

and antivirals such as acyclovir, valacyclovir, famciclovir or foscarnet can be administered in selected cases (43).

Epstein-Barr virus

The Epstein-Barr virus (EBV) is part of the *Gammaherpesvirinae* subfamily, and it presents a particular tropism for B cells. The virus is ubiquitous, and over 90% of the general population has a positive serology for EBV (44). Infectious mononucleosis is the acute infection (45), when the virus establishes a cellular latency reservoir, its genome changing its shape to become circular, episomal, embedded in the nucleus of memory B cells (44). Apart from the well-described latency in B cells, recent laboratory studies have reported EBV-2 latency in T cells (46).

EBV latency has been associated with multiple neoplastic disorders (Burkitt lymphoma, nasopharyngeal carcinoma of lymphoproliferative disorders) as well as autoimmune diseases (47-49), being a potential trigger for RA (50,51).

The incidence of lymphoma in patients with RA is twice as high compared to the general population (52). It is currently unclear whether treatment with anti-TNF-α additionally increases this risk through reactivation of latent EBV infection.

Balandraud et al. (53) have reported that patients with RA display EBV peripheral blood mononuclear cells viremia (16 copies/500 ng DNA) 10 times higher than the control group, this increase being directly correlated to disease activity. Follow-up data for over 4 years has shown that treatment with anti-TNF-α agents (infliximab or etanercept) does not significantly influence viral load. Askling et al. (54), after analyzing 6,604 patients from the Swedish Biologics Register (ARTIS), concluded that TNF antagonists do not influence the incidence of lymphoma in patients with RA.

However, a different study showed that viral load monitoring could select patients susceptible to developing lymphoma, with values above 500 copies/500 ng DNA pointing to potential evolution towards lymphoproliferative disease (52). Park et al. (55) have described a case of diffuse lymphoproliferative disease associated with EBV infection, that developed shortly after the initiation of etanercept treatment in a patient with RA, and that regressed spontaneously after discontinuation of biological therapy.

Colaci et al. (56) report reactivation of EBV infection in a patient with RA, 11 days after the first dose of infliximab, with spontaneous remission of symptoms over the course of 5 days; in this case treatment was continued after a time span of 4 weeks, without further events. Ueda et al. (57) describe EBV reactivation leading to acute disseminated encephalomyelitis in a patient receiving infliximab for Crohn's disease.

Acute EBV infection does not require specific antiviral treatment due to its self-limiting evolution (58); antivirals such as acyclovir or ganciclovir can be used in cases with severe outlines (18). Discontinuing anti-TNF agents should be considered in severe cases of EBV-associated illness (18).

There is no currently approved vaccine against EBV, but there is dire need for developing one, since this particular virus is linked to 200,000 new cases of neoplastic disease each year (59).

Cytomegalovirus

Cytomegalovirus (CMV) is a common pathogen belonging to the *Betaherpesvirinae* subfamily and is transmitted by direct contact with bodily fluids.

Seroprevalence studies suggest that by the time they reach adolescence, 10-20% of the population has already been exposed to CMV infection, the percentage increasing to 40-100% in adult population (18).

The primary infection in immunocompetent patients is commonly asymptomatic, but it can also display a mononucleosis-like outline, with the virus subsequently remaining latent in CD34+ progenitor myeloid cells (60) and in monocytes/macrophages (61). CMV persistence has also been associated with immunosenescence (62).

Reactivation of latent infection in immunosuppressed patients can virtually affect any system of the human body, with frequent case reports of encephalitis, pneumonia, enterocolitis, hepatitis or retinitis in HIV-positive patients (18,60). CMV has also been incriminated as potential trigger in autoimmune diseases (60) such as systemic lupus erythematosus (SLE) and RA.

CMV infection reactivation in patients undergoing anti-TNF-α therapy has been documented in a series of case reports (63-65). Petersen et al. (65) describe 2 cases of CMV infection secondary to etanercept and efalizumab therapy, respectively. Both cases were characterized by a prolonged evolution, with complains of severe fatigue in addition to other symptoms. Le Clech et al. (66) present a case of se-

vere CMV infection in a patient with cancer undergoing maintenance treatment with rituximab.

However, the study performed by Davignon et al. (67) showed that the CD4+ T cell response to CMV is not influenced by treatment with anti-TNF-α agents and that the infection remains under control even in patients with RA undergoing anti-TNF-α therapy. Torre-Cisneros et al. (68) prospectively followed 15 patients with RA treated with infliximab, over the course of the first 6 weeks of therapy, with the purpose of evaluating the reactivation of CMV, EBV or human herpes viruses (HHV) 6, 7 and 8. No signs of reactivation or primary infection were detected in this study.

Patients that are asymptomatic or display mild disease do not require specific therapy and do not present a contraindication for continuing the anti-TNF treatment. In severe cases however, biological therapy should be discontinued until symptoms' resolution and antiviral therapy should be considered (18). Therapeutic options include ganciclovir, and valganciclovir or foscarnet in case of resistance or intolerance to ganciclovir (18).

Human herpes virus 8

Human herpes virus 8 (also known as Kaposi's sarcoma-associated herpes virus – KSHV) belongs to the subfamily *Gammaherpesvirinae* and represents the infectious agent underlying Kaposi's disease (KD) and other lymphoproliferative diseases such as primary effusion lymphomas and multicentric Castelman's disease (69). This is why the virus is also named Kaposi's Sarcoma-Associated Herpes virus (KSHV) (70,71).

The exact transmission routes for HHV-8 are not fully understood. Both sexual and non-sexual transmission has been described (69), HHV-8 having been detected in saliva, prostatic fluid, blood products or transplanted organs (70). Latency is established through a dramatic change in the viral genome, from an initial histone-free outline, to a multi-copy histone-packed episomal chromatin structure (72), circularized and tethered to host chromosomes by the viral latency-associated nuclear antigen (LANA) (73). LANA also facilitates latency and stimulates the proliferation of latently-infected cells through an upregulation of survivin, an inhibitor of apoptosis (74). Viral infection of endothelial cells is associated with KD, while infection of B cells is linked to the above-referenced lymphoproliferative disorders (70).

Unlike EBV and CMV, two other viruses belonging to the *Herpesviridae* family, HHV-8 does not seem to be involved in the pathogenesis of autoimmune diseases and does not represent a possible trigger for such conditions (75).

Although HHV-8 infection represents a trigger for KD, other co-factors are also needed, namely immunosuppression secondary to HIV infection or post-organ transplant (76). KD can also be observed in elderly persons without other apparent causes of immunodepression.

Field literature data is scarce and cannot support the role of biological therapy in the reactivation of latent infection with HHV-8.

Lavagna et al. (77), having prospectively followed for 14 weeks 60 patients with Crohn's disease undergoing treatment with infliximab, have not recorded any cases of reactivation of HHV-8 infection. Nicoli et al. (78) present safety and efficacy data for rituximab in the treatment of multicentric Castelman disease. Other case reports describe the use of tocilizumab in the treatment of iatrogenic KD in a patient with RA (79), or in treatment of multicentric Castelman disease (80).

On the other hand, field literature describes cases of KD secondary to infliximab (81), adalimumab (82) or rituximab (59,83) treatment. Martinez et al. (84) report a KD case that started 10 days after the second dose of infliximab in an HIV-negative patient with corticodependent Crohn's disease; following discontinuation of infliximab, an improvement in KD skin lesions was observed.

Human papilloma virus

Human papilloma virus (HPV) belongs to the *Papillomaviridae* family and is a sexually transmitted virus. Most infections with HPV are subclinical (85), and 80% of cases display a self-limiting evolution within one year, as a result of cellular immune response (86). Several viral subtypes have been identified, with different clinical evolution. For example, subtypes 1, 2, 4, 6, and 11 are associated with low risk of malignant transformation, causing benign cutaneous warts or condyloma acuminata, while subtypes 16, 18, 30, 31 are associated with cervical dysplasia, cervical cancer, and rectal, penile, vulvar, vaginal or oropharyngeal carcinoma (18).

So far, the exact mechanisms whereby HPV establishes latency reservoirs have not been identified,

but one hypothesis describes viral latency in basal epithelial stem cells, whose binary division leaves a copy of the virus-infected cell in the basal layer, while the daughter-cell undergoes terminal differentiation (87). Maglennon et al. (88) also describe the phenomenon of immune-mediated latency in epithelial cells that do not sustain the complete virus life cycle.

At the moment, there is very little data on the incidence and prevalence of HPV infection in patients with rheumatic conditions, despite the fact that HPV infection is the most frequent sexually-transmitted disease in the United States (85,86).

A recent study by Waisberg et al. (89) evaluated HPV and *Chlamydia trachomatis* infections in patients with RA pre- and post- anti-TNF-α therapy, and concluded that in the short term this treatment does not appear to increase the risk of HPV infection evolution in this category of patients. However, Georgala et al. (90) reported a potential association between anti-TNF-α agents and progression of HPV infection by describing 3 cases with fast progression of cytological lesions; for this reason they recommend a routine Pap smear, before, during and after treatment.

In conclusion, although limited, literature data indicate a possible association between immunosuppressive therapy and persistent HPV infection with a risk of progression towards a neoplastic pathology. Future studies are needed to determine the optimal screening strategy for HPV infection before starting biological therapy, and to evaluate the benefit of anti-HPV vaccination in immunosuppressed patients (85).

Polyomavirus – JC

JC virus (JCV) is a DNA virus, part of the *Polyomaviridae* genus, *Papovaviridae* family (91). Primary infection takes place early during childhood by respiratory or urinary-oral transmission and is asymptomatic (92). The main latency reservoir for the circular episomal form of JCV is represented by renal epithelial cells (93) and urothelial cells, however, there are clues as to the latency or persistence of the virus in B lymphocytes, spleen (94), tonsils (95), lymph nodes (96), or bone marrow (97). The two main pathologies determined by the reactivation of JCV include polyomavirus-associated nephropathy (particularly in patients with kidney or other organ post-transplant status) (94) and progressive multifocal leukoencephalitis (PML), a rare and usually fatal condition of the central nervous system, which requires the reactivation of JCV with neuroadaptation (95) leading to viral cytolytic replication in oligodendrocytes, thereby determining multiple demyelination foci (98).

Even though most cases of PML have been described in patients with severe immunosuppression, such as AIDS stage HIV infection, neoplasia or post-organ transplant (92), the association between this condition and biological therapy has become widely known after several PML cases were reported in patients who received natalizumab, a monoclonal antibody directed against α4 integrin, that is used in the treatment of multiple sclerosis (99) and Crohn's disease (100). Another biologic agent that has been associated with this pathology is efalizumab (used in the treatment of psoriasis) (101).

The use of biological therapy in rheumatic conditions has led to the reporting of such reactivation cases in patients with RA or SLE under treatment with monoclonal antibodies such as rituximab (102-106) or tocilizumab (107).

A retrospective cohort study that included 734 patients with inflammatory bowel disease undergoing treatment with infliximab has described a fatal case of PML after use of natalizumab and infliximab (108). Also, Yamamoto et al. (109) have reported a case of PML in a patient with RA under treatment with etanercept; even though this patient exhibited characteristic symptoms for PML, PCR for JCV DNA in the cerebrospinal fluid was negative.

In conclusion, PML is a rare complication with unfavorable prognosis. Because the diagnosis of PML is hard to establish and the most important therapeutic intervention requires reduction of immunosuppression status (110), this etiology has to be considered in any immunosuppressed patient who develops new neurologic symptoms such as disorientation, ataxia, speech disorders or vision impairment (85).

CONCLUSIONS

Patients undergoing treatment with the currently available biologics are at high risk for reactivation of latent viral infections. Such patients should therefore undergo thorough screening prior to the initiation of therapy, including checking and updating the patients' vaccination status. If found positive for latent viral infections, these patients might benefit from prophylactic antiviral therapy. Clinicians monitoring

patients in treatment with biologics should be aware that viral infections may display an atypical presentation. Currently available literature data is scarce, and does not present sufficient information derived from comparative studies, in order to determine the best choice of biologics from an infectious risk perspective.

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