Absence of Varicella Zoster Virus Reactivation after Infliximab Administration for Plaque Psoriasis

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Introduction
The incidence of severe, extensive and longstanding cases of cutaneous herpes zoster (HZ) is clearly increased in patients receiving tumor necrosis factor (TNF) antagonists [1, 2]. This may occur either with the antibodies infliximab and adalimumab or the receptor antagonist etanercept [2]. In contrast, the effect of TNF antagonists on the incidence of HZ still remains debated in the literature, varying from no significant impact [3, 4] to a 2- to 4-fold increase [1, 2]. The precise impact of TNF antagonists on varicella zoster virus (VZV) reactivation remains unclear. Subclinical VZV viremia represents a marker of VZV reactivation and is detected occasionally (0–9%) in immunocompetent and immunosuppressed subjects without active VZV disease [5], in some patients with active HZ [6, 7] and more frequently in immunosuppressed patients with HZ [7].

This pilot study evaluated whether the administration of a TNF antagonist may reactivate VZV and lead to a detectable VZV load assessed by real-time polymerase chain reaction (rt-PCR).
Subjects and Methods

A pilot cohort of six patients with longstanding and extensive psoriasis treated with infliximab, a chimeric anti-TNFα antibody (Remicade®; MSD), was selected. Patient demographics are presented in table 1. This pilot study was performed in accordance with the ethical standards of the University Hospital Committee on Institutional Human Experimentation and with the Helsinki Declaration of 1975, as amended in 1983. The aims of the study and all the procedures were explained to the patients and they all signed an informed consent. All patients were specific VZV IgG+, IgM– and herpes simplex virus IgG+, IgM–, as determined by ELISA. None of the patients had a history of previous HZ, but all recalled varicella. None of the patients had ever received the OKA strain vaccination for varicella or the HZ vaccination (Zostavax®).

The patients did not receive concomitant other anti-psoriasis agents such as methotrexate, cyclosporine or acitretin. Patients with varicella (n = 5), HZ (n = 5) and normal subjects (n = 5) were included as controls.

Blood samples were taken on day 1 (before infliximab administration) and on days 2, 7, 21 and 42 for the determination of VZV viremia by an ORF21 rt-PCR-based assay, performed according to a previously published protocol [8]. Blood samples were collected on EDTA tubes and plasma stored at –20 °C. Automated DNA extractions were performed on plasma (300 μl) using the Maxwell16 Cell LEV Total RNA purification kit (Promega). An internal control (DNA Virus Culture, Diagenode) was added to each sample before extraction. DNA was eluted in pure-grade water (50 μl). rt-PCR was performed using VZV gene 21-specific primers and FAM probes as described previously (synthesized by Eurogentec). Reactions were performed in 25 μl volumes containing Mastermix and Smart cycler buffer (Diagenode), Double Dye Probe and Primer TR mix (Diagenode) for internal control amplification and detection, VZV 21 primers (300 nM final concentration), VZV 21 probe (100 nM final concentration) and 5 μl of eluted DNA. rt-PCR amplification and detection was performed using a Smartcycler V2 system (Cepheid). The lower limit of detection was 20 viral copies/ml. For quantification, relative copy numbers were calculated from standard curves generated in each PCR run using AcroMetrix VZV high plasma control (AcroMetrix) diluted in negative plasma. The standard curves were highly reproducible.

Results

In none of the infliximab-treated psoriasis patients and at none of the five successive time points was any VZV viral load detected. Of the five HZ patients, two presented VZV viremia with 40 and 49 viral copies/ml. All the patients with varicella presented VZV viremia (mean 61,035 copies/ml, range 1,835–107,673). In the normal controls no VZV viremia was detected.

Discussion

The severity, extension and duration of HZ is principally related to the degree of immunodeficiency, evidenced by increased severity among subjects with lymphoproliferative diseases, bone marrow or organ transplantations and AIDS [9]. TNF antagonists have a proven effect on the severity of HZ [1, 2] and probably affect its incidence [3, 4]. In this pilot study there was no evidence that intravenous infliximab administration in psoriasis patients resulted in a detectable VZV subclinical viremia at any time point. Although the number of patients is limited, this fact might favor the hypothesis that the variations of the incidence of HZ in patients receiving TNF antagonists are rather due to methodological study biases than to an influence of TNF antagonists on VZV reactivation. These studies are indeed difficult to interpret as multiple variables intervene, such as age, drug exposure, concomitant drug exposure, etc.

The increased incidence of severe, extensive and longstanding cutaneous lesions of HZ in patients receiving TNF antagonist may be linked to the critical roles of TNFα and interferon-γ in the control of viral infections, by recruiting and activating T cells, natural killer cells and

Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Weight</th>
<th>Infliximab dose</th>
<th>Type of psoriasis</th>
<th>Psoriasis since</th>
<th>Infliximab exposure before testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>m</td>
<td>78 kg</td>
<td>400 mg</td>
<td>plaque guttata</td>
<td>2000</td>
<td>84 months</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>m</td>
<td>76 kg</td>
<td>400 mg</td>
<td>plaque</td>
<td>1978</td>
<td>70 months</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>m</td>
<td>87 kg</td>
<td>500 mg</td>
<td>plaque</td>
<td>2007</td>
<td>35 months</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>m</td>
<td>93 kg</td>
<td>500 mg</td>
<td>plaque guttata</td>
<td>2005</td>
<td>48 months</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>m</td>
<td>97 kg</td>
<td>600 mg</td>
<td>plaque</td>
<td>1983</td>
<td>30 months</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>f</td>
<td>101 kg</td>
<td>500 mg</td>
<td>plaque</td>
<td>2005</td>
<td>36 months</td>
</tr>
</tbody>
</table>

*Plus methotrexate 12.5 mg/week.
macrophages, hence impairing the cutaneous immune response against the VZV infection [10, 11].

In terms of clinical management, these facts should alert the physician to the potential increased severity of HZ in patients receiving TNF antagonists and accordingly lead to treatment with antivirals. HZ vaccination should be recommended before initiating TNF antagonists.

**Disclosure Statement**

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**References**