Cutaneous injection site reactions to long-term therapy with enfuvirtide

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Objective: Enfuvirtide is the first of a new class of antiretroviral agents. The drug is safe and well tolerated; injection site reactions are the most common adverse events. The aim of this study was the clinical and histopathological evaluation of injection site reactions in patients treated for 80 weeks.

Materials and methods: Six patients were evaluated. Five of them underwent cutaneous biopsies using a 4 mm punch. Sections were stained with haematoxylin–eosin, periodic acid-Schiff stain and Verhoeff’s stain. Moreover, immunohistochemical studies were carried out using CD20, CD45Ro and CD34 antibodies.

Results: Four different macroscopic patterns were presented: (a) no evidence of cutaneous lesions; (b) transient infiltrative lesions which auto-resolved within 24 h; (c) transient nodular lesions which auto-resolved within 7–15 days; and (d) stable lesions after more than 30 days with a scleroderma-like aspect. Histological examination showed three patterns: (1) an acute urticaria/vasculitis-like pattern with inflammation of the fat tissue; (2) a sub-acute pattern with an initial dermal sclerosis; (3) a chronic scleroderma-like pattern with connective tissue disposed around the adnexa, whose structure was intact. The immunohistochemical study evidenced a prevalence of T lymphocytes and a moderate neoangiogenesis.

Conclusions: In our experience, after a rather long period of treatment, cutaneous reactions comprised a variety of features largely independent of the virological and immunological outcome. The adnexa was unaltered in all patients, this indicating a tendency to a possible regression of the sclerotic lesions. Therefore, patients should be encouraged to rotate the sites of injection thus permitting the tissues to regenerate.

Keywords: antiretroviral therapy, HIV-1 fusion inhibitors, peptide inhibitors

Introduction

Although considerable advances have been made in antiretroviral therapies for treatment of HIV, new therapeutic options are necessary to overcome resistant viral strains or intolerance to existing drugs. Enfuvirtide is an antiretroviral peptide drug, derived from the heptad repeat 2 (HR2) domain of the GP41. This drug is the first of a new class of agents called HIV-1 fusion inhibitors that block the fusion of the viral particle with the host target cell. Previous studies have shown that enfuvirtide is safe and well tolerated; injection site reactions (ISRs) are the most common adverse events associated with the administration of this drug.1–4

The aim of this study was the clinical and histopathological evaluation of ISRs in patients treated with enfuvirtide for 80 weeks.

Materials and methods

Six patients being treated with enfuvirtide-based antiretroviral therapy for more than 80 weeks were evaluated. Patients were enrolled in the TORO2 trial conducted in Europe and Australia.5 The trial assigned patients with previous treatment with each of the three classes of antiretroviral drugs, and/or documented resistance to each class (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors) to receive randomly either enfuvirtide (90 mg twice daily) plus a background regimen optimized with the aid of resistance testing (enfuvirtide group) or the background regimen alone (control group). At 24 weeks, TORO 2 showed a significant decrease in the plasma viral load in the enfuvirtide group (least squares mean change from baseline 1.429 log10 per mL), compared to 0.648 log10 per mL in the control group. The mean increase in the CD4 cell count was greater in the enfuvirtide group (65.5 cells/mm3) than in the control group (38.0 cells/mm3). Similar results were found in the TORO1 study, conducted in North America, Mexico and Brazil.6

Epidemiological, immunological and virological data at baseline, together with the optimized background (OB) of the six patients are summarized in Table 1. Five of the six patients underwent cutaneous biopsies using a 4 mm punch (PDM GmbH, Köln/Surth, Germany). The samples were fixed in 10% buffered formalin and paraffin-embedded.

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JAC vol.53 no.4 © The British Society for Antimicrobial Chemotherapy 2004; all rights reserved.
micrometre sections were stained with haematoxylin–eosin, periodic acid-Schiff stain and Verhoeff’s stain for the study of the elastic fibres. Moreover, to investigate the lymphocytic infiltration and neoangiogenesis, immunohistochemical studies were carried out using CD20 (clone L26, DAKO s.p.a., Milan, Italy), CD45Ro (clone UCHL1, DAKO s.p.a., Milan, Italy) and CD34 antibodies (QBEND10, Bio Optica, Milan, Italy).

**Results**

After punch-biopsy assessment, four different macroscopic patterns were presented by the patients: (a) no evidence of cutaneous lesions (one patient); (b) transient infiltrative lesions which auto-resolved within 24 h (one patient); (c) transient nodular lesions which auto-resolved within 7–15 days (one patient); and (d) stable lesions after more than 30 days with a scleroderma-like aspect (three patients).

Of the six patients, only one without clinical lesions denied consent for the punch biopsy. In the patient with clinical pattern (b), the biopsy was carried out 12 h after injection at that site; in the patient with pattern (c) after 7 days and in the three patients with pattern (d) after 1 month.

Histological examination carried out on the remaining five patients showed three distinct morphological patterns: (1) within 12 h after the inoculation (patient 1), an acute urticaria/vasculitis-like pattern characterized by polymorphic inflammatory infiltration with a rich eosinophil component, especially around the vessels was observed in addition to involvement of the fat tissue with interstitial and lobular inflammation; (2) a sub-acute pattern characterized by moderate lymphocytic infiltration, particularly around the vessels, and an initial derma sclerosis was observed after 7 days from inoculation (patient 6); (3) a chronic scleroderma-like pattern was characterized by absence of inflammatory infiltration and progressive sclerosis of the derma; in the latter, connective tissue was typically disposed around the adnexa, whose structure was intact (patients 3, 5 and 2).

In all patients, the immunohistochemical study showed a prevalence of T lymphocytes (CD45Ro) on B lymphocytes (CD20) and a moderate neoangiogenesis (CD34).

**Discussion**

Enfuvirtide is the first molecule of the new class of entry inhibitors. These antiretrovirals prevent fusion of HIV-1 to CD4 cells by inhibiting the action of the gp41 trans-membrane glycoprotein thus blocking the structural changes required for membrane fusion. As the drug is a synthetic protein, it must be administrated by subcutaneous injection. The enfuvirtide dose regimen selected for use according to recent studies is 90 mg twice daily. Absorption profiles from the abdomen, thigh and arm are comparable, therefore the sites of injection can be rotated providing greater flexibility in enfuvirtide administration.

The analysis of data from a Phase III study has shown that ISRs occur in 97.9% of patients. In most patients (85.6%), the reaction appears during the first week of treatment. These reactions generally did not worsen over time and few patients had infections at the injection site. In total, 1–3% of patients had severe pain which limited normal activities and required analgesics. Average duration of an individual ISR was about 7 days. Treatment discontinuation rate as a result of ISRs was 3% and less than 1% of patients discontinued therapy because of difficulty with self-administered injections. The most frequent signs and symptoms of a local ISR were pain and/or discomfort.
### Table 2. Histological results of the biopsies of the ISRs

<table>
<thead>
<tr>
<th>Patients</th>
<th>Epidermis</th>
<th>Dermis</th>
<th>Infiltration</th>
<th>CD20</th>
<th>CD45Ro</th>
<th>CD34</th>
<th>Vessels</th>
<th>Subcutaneous</th>
<th>Adnexa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>moderately</td>
<td>elastic fibres</td>
<td>fragmented</td>
<td>focal presence</td>
<td>diffuse presence</td>
<td>diffuse presence</td>
<td>no neoangiogenesis, but vasculitis of the vessels with little and median gauge; depositions of eosinophils in the lumen of a median gauge vessel</td>
<td>lobular panniculitis</td>
<td>normal</td>
</tr>
<tr>
<td>2</td>
<td>atrophic</td>
<td>thickness and gross aggregation of the collagen fibres; elastic fibres fragmented</td>
<td>massive; mainly lymphocytic, with eosinophils; perivascular and diffused</td>
<td>focal presence</td>
<td>diffuse presence</td>
<td>diffuse presence</td>
<td>moderate neoangiogenesis</td>
<td>moderate interstitial inflammation</td>
<td>normal</td>
</tr>
<tr>
<td>3</td>
<td>normal</td>
<td>thickness and gross aggregation of the collagen fibres; elastic fibres fragmented</td>
<td>moderate; lymphocytic; diffused</td>
<td>not evaluable</td>
<td>not evaluable</td>
<td>negative</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>5</td>
<td>normal</td>
<td>thickness and gross aggregation of the collagen fibres; elastic fibres fragmented</td>
<td>moderate; lymphocytic; diffused</td>
<td>not evaluable</td>
<td>not evaluable</td>
<td>not evaluable</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>6</td>
<td>thin and</td>
<td>moderate thickness of the collagen fibres; elastic fibres fragmented</td>
<td>intermediate; lymphocytic; dermal, perivascular and diffused</td>
<td>focal presence</td>
<td>diffuse presence</td>
<td>focal presence</td>
<td>moderate neoangiogenesis</td>
<td>normal</td>
<td>normal</td>
</tr>
</tbody>
</table>
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In conclusion, although observations on larger patient samples are warranted, our data seem to indicate that a wide array of responses to ISRs can be observed and that an iatrogenic scleroderma is not the rule, even with long-term follow-up.

Acknowledgements

We are grateful to Ms Paulene Butts for her assistance in the preparation of the manuscript.

References


