Post Marketing Surveillance on Safety and Efficacy of IMOD in Iranian Patients with HIV/AIDS

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Abstract

Acquired Immune Deficiency Syndrome is one of the world’s serious health problems. Immune-based therapy is a new approach in the treatment of HIV infected patients. IMOD™ with the ability to correct immune deficiencies has been introduced for the management of HIV infection. In the phase IV trial study the main objectives were to assess the possible side effects, evaluate its effect on CD4+ T Lymphocyte count and patients’ and physicians’ satisfaction of 600 HIV infected patients in 13 centers during 2007. The observed adverse events in patients included: headache and vertigo (1.2%), nausea (1.2%), gastritis (1.2%), phlebitis (1%) and mild rash (1%); serious adverse events were not observed in any of IMODTM recipients. Therefore it was not needed to terminate the treatment in any of patient. The results of this study demonstrated that daily prescription of IMOD™ significantly increases T Lymphocyte CD4+ and Total Lymphocyte Count in HIV-positive patients. In addition, nearly 90% of the patients and 70% physicians are satisfied by IMOD™ treatment.

Keywords: Post marketing surveillance; Safety; Efficacy; Satisfaction; Side effect; MOD™

Background

Human Immunodeficiency Virus (HIV) primarily targets CD4+ lymphocytes, provoking Acquired Immunodeficiency Syndrome (AIDS) and subsequent immunosuppression that results in evolution of opportunistic infections [1,2].

Although Highly Active Anti-Retroviral Therapy (HAART) is the principal management strategy in patients with HIV infection, adverse effects, drug reactions, resistance, toxicities and psychological issues may lead to treatment failure, especially in developing countries [3-5]. Immune-based therapy is a new approach in the treatment of HIV infected a patient which has been developed in the past few years [6].

MOD™ is a safe and effective herbal and immunomodulator drug that was firstly introduced for treatment of HIV infection in Iran in 2006. Its profile has been evaluated and approved by legal committee for drug production of The Ministry of Health and Medical Education of Iran [7].

It is basically composed of a mixture of herbal extracts, selenium, carotene and flavenoids [7]. It has been shown that MOD™ induces production of Interferon-γ and Interleukin-2. Except for mild sweating and weight loss, no specific adverse effect, dose-limiting toxicity or any alterations in patient’s coagulability state have been addressed in patients taking MOD™ so far [8-11].

Since side effects influence patients’ and physicians’ satisfaction, and subsequently the satisfaction had a significant effect on adherence to drug treatment [12], we therefore conducted this study to assess the possible side effects and complications that may happen throughout the treatment period by MOD™ and also to evaluate its effect on CD4+ T Lymphocyte count and patients’ and physicians’ satisfaction in HIV infected individuals.

Methods

Study design

In phase IV trial with the aim of evaluating the safety and effectiveness of IMOD, we recorded the outcomes of 600 HIV/AIDS patients who were treated simultaneously in 13 Voluntary and Counseling Testing (VCT) centers including Tehran, Shiraz, Kermanshah, Khoram Abad, Borujerdi, Mashhad, Isfahan, Kerman, Zahedan, Arak, Boushehr, Bandar-Abbas and Gorgan during 2007. Infectious disease specialists, general practitioners and other staff of the centers were trained for the necessary skills at the first stage. The treatment for HIV/AIDS patients was initiated according to the approved protocol of Iranian Research Center for HIV/AIDS (IRCHA).

All the adverse events were recorded while patients were receiving IMOD. Adverse drug reactions were recorded in an electronic database via specific website designed for this purpose. These patients were registered in the website: http://www.ADR.ir; where their demographic and therapeutic features (city or center of drug consumption, age, sex, CD4+ count and TLC) in addition to evolved adverse effects have also been recorded. Furthermore effectiveness was reassessed through monitoring the patients and comparing their blood T Lymphocyte...
CD4+ or Total Lymphocyte Count (TLC) indices before and after treatment.

Inclusion and exclusion criteria

Each HIV positive person who agreed to receive MOD™ was included. Patients, who were taking anti-retroviral medications, continued their standard treatment with MOD™. During this period, no patient was deprived from anti-retroviral medications if needed.

We planned to exclude patients who had any serious adverse event related to MOD™ or who did not interested to continue their treatment.

Treatment protocols

The treatment protocol was intravenous administration of a vial of MOD™ (4 ml containing 100 mg active ingredient) in 100 ml D/W 5% during 30 minutes every day for three months.

T lymphocyte assessment

For all patients CD4+ count was measured before and after administration of MOD™. Count of T Lymphocyte CD4+ was measured if the Flow Cytometry instrument was available. In other centers Total Lymphocyte Count (TLC) was considered as an alternative method. The analyses of MOD™ effectiveness in all patients and in subgroups were separately performed based on the counts of T Lymphocyte CD4+ (<200, between 200 and 400) and TLC (<1200, between 1200 and 2600).

Satisfaction

Patients’ and physicians’ satisfactions were evaluated through a questionnaire measuring the overall treatment satisfaction based on a 10 point likert scale. Zero representing least and 10 representing the highest levels of satisfaction.

Statistical analyses

Statistical analyses of the results were performed using SPSS for windows, release 11.5 (SPSS .Inc) and data are presented as means ± standard deviations (SD). Paired t-test was used for comparison between pre- and post-treatment results and P-values<0.05 were considered statistically significant. According to the count of T Lymphocyte CD4+ or Total Lymphocyte Count (TLC), subgroup analysis was performed.

Results

Assessment of adverse events

A total of 600 HIV-positive patients were enrolled in our study. During the course of treatment, ninety doses of MOD™ were administered to each patient; thus more than 54000 MOD™ injections were separately performed based on the counts of T Lymphocyte CD4+

Effectiveness

To assess the effectiveness of MOD™, changes in count of CD4+ lymphocyte cells were analyzed as a major outcome. If lymphocyte counter did not exist in a center, TLC was considered as an alternative for patient’s recruitments and post-treatment analysis (58% of cases).

Pre- and post-treatment evaluations of T Lymphocyte CD4+ and TLC have been illustrated in tables 1 and 2. Our data showed a statistically significant increase in T Lymphocyte CD4+ count and TLC after MOD™ administration.

Satisfaction

The mean of satisfaction score for physicians and patients were 7.2 (SD=3.4) and 8.8 (SD=2.1), respectively. As shown in figure 1, the results for treatment satisfaction analysis were separated into satisfied and unsatisfied groups of physicians and patients.

Discussion

Our study indicated that only 6% of patients complained from adverse effects. Also, the results of this study demonstrated that the daily prescription of MOD™ significantly increases T Lymphocyte CD4+ and TLC in HIV-positive patients. In addition, the most of the patients (90%) and physicians (70%) are satisfied by MOD™ treatment.

Table 1: The difference between means of T Lymphocyte CD4+ counts pre- and post- treatment in all patients, in patients having T Lymphocyte CD4+ count less than 200 cells/mm³ and in patients with Total Lymphocyte Count between 200 and 400 cells/mm³.

<table>
<thead>
<tr>
<th>T Lymphocyte CD4+ count</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>320 ± 28</td>
<td>392 ± 30</td>
<td>0.000</td>
</tr>
<tr>
<td>Patients having T Lymphocyte CD4+ count less than 200</td>
<td>109 ± 26</td>
<td>236 ± 70</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients with T Lymphocyte CD4+ count between 200 and 400</td>
<td>296 ± 20</td>
<td>378 ± 68</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Table 2: The difference between means of TLC pre- and post- treatment in all patients, patients having TLC less than 200 cells/mm³ and patients with TLC between 1200 and 2600 cells/mm³.

<table>
<thead>
<tr>
<th>Total Lymphocyte Count</th>
<th>First TLC</th>
<th>Last TLC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2094 ± 194</td>
<td>2747 ± 204</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients with TLC &lt; 1200</td>
<td>923 ± 294</td>
<td>1948 ± 482</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients with TLC ≥ 1200 &lt; 2600</td>
<td>1759 ± 100</td>
<td>2310 ± 230</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Figure 1: The overall treatment satisfaction declared by physicians and patients.
The use of HAART has been associated with several adverse effects and toxicities including hypersensitivity reactions, neurotoxicity, nephropathy, liver damage, body fat redistribution syndrome and different metabolic alterations. Severe life threatening conditions including lactic acidosis, hepatitis, drug reactions and cardiovascular diseases have also been reported [13,14]. Moreover, increasing resistance to HAART limits its effectiveness [15-17]. Developing nations should also face the high costs to provide standard antiretroviral treatments for their HIV patients [18].

One study has shown that 50-70% of patients with HIV/AIDS who were taking HAART experienced problems with adverse effects and thus did not adhere to their medications. Evolution of these symptoms resulted in losing confidence, discontinuation of drug intake and altering time or dosage of medication without consulting to their physicians. Subsequently, this inappropriate adherence to HAART may lead to CD4+ decline and poor treatment results [19-21].

MOD™ is a safe immunomodulator drug and no serious side effect has been observed in patients who received it in previous clinical trials [22]. In fact, results show that MOD™ is a low-toxic drug; and no significant change occurred in hematological and biochemical profiles of experimental animals. The drug did not cause any undesirable effects on protein, carbohydrate and lipid metabolisms. Liver enzymes activity and bilirubin levels did not show significant changes. Moreover, lack of considerable changes in urea and creatinine levels revealed that CD4+ did not pose any damaging effect on the excretory function of kidneys in experimental animals [22].

Limitations of HAART could be partly explained by extremely high rates of mutations in the virus’ antigenic structure; thereby, introduction of novel drugs such as MOD™ with immunity stimulating properties may significantly contribute to pain relief in HIV patients [11]. In addition, results of our study introduce a potentially effective treatment for HIV patients with minimal side effects.

Considering the high costs and side effects of the available standard drugs and their significant burden on the health systems in developing countries, MOD™ may be used as the first line of treatment in developing countries [11].

A series of determinants affect patient’s satisfaction from treatment including patient opinion from hospital care in HIV services, hospital environment as well as major problem areas such as pain management, education about side effects, depression and poor health-related quality of life. Therefore these factors should be considered as indicators of provided care quality and the need for further intervention. Doctor’s satisfaction is also scaled via patient’s satisfaction from treatment, work content, peer recognition, patient’s family support and work environment [12].

Regarding high levels of patients’ and physicians’ satisfaction in combination with its safety and efficacy, we propose IMOD™ as the drug of choice for treatment of patients with HIV/AIDS in Iran.

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References