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The Adverse Event Profile in Patients Treated with Transferon™ (Dialyzable Leukocyte Extracts): A Preliminary Report

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Abstract

Background: Dialyzable leukocyte extracts (DLE) are heterogeneous mixtures of peptides less than 10 kDa in size that are used as immunomodulatory adjuvants in immune-mediated diseases. Transferon™ is DLE manufactured by National Polytechnic Institute (IPN), and is registered by Mexican health-regulatory authorities as an immunomodulatory drug and commercialized nationally. The proposed mechanism of action of Transferon™ is induction of a Th1 immunoregulatory response. Despite that it is widely used, to date there are no reports of adverse events related to the clinical safety of human DLE or Transferon™. Objective: To assess the safety of Transferon™ in a large group of patients exposed to DLE as adjuvant treatment. Methods: We included in this study 3844 patients from our Clinical Immunology Service at the Unit of External Services and Clinical Research (USEIC), IPN. Analysis was performed from January 2014 to November 2014, searching for clinical adverse events in patients with immune-mediated diseases and treated with

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Transferon™ as an adjuvant. Results: In this work we observed clinical nonserious adverse events (AE) in 1.9% of patients treated with Transferon™ (MD 1.9, IQR 1.7 - 2.0). AE were 2.8 times more frequently observed in female than in male patients. The most common AE were headache in 15.7%, followed by rash in 11.4%, increased disease-related symptomatology in 10%, rhinorrhea in 7.1%, cough in 5.7%, and fatigue in 5.7% of patients with AE. 63% of adverse event presentation occurred from day 1 to day 4 of treatment with Transferon™, and mean time resolution of adverse events was 14 days. In 23 cases, the therapy was stopped because of adverse events and no serious adverse events were observed in this study. Conclusion: Transferon™ induced low frequency of nonserious adverse events during adjuvant treatment. Further monitoring is advisable for different age and disease groups of patients.

Keywords

Dialyzable Leukocyte Extracts, Adverse Events, Monitoring, Drug Safety, Adjuvant Therapy, Immunoregulation, Guidelines, Transfer Factor, Pharmacovigilance

1. Introduction

Dialyzable leukocyte extracts (DLE) are heterogeneous mixtures of peptides under 10 kDa, released after disruption of peripheral blood leukocytes from healthy donors [1]. It has been reported that administration of DLE improves clinical responses in allergies [2], in infections and immunodeficiency syndromes [3]-[5], and in some other immune-mediated diseases (reviewed in [6]). The therapeutic adjuvant effect of DLE is associated with their ability to modulate immune responses changing innate signaling pathways, such as TLRs [7], NF-kB, and cyclic adenosine monophosphate (cAMP) in cultured cells [8] [9]; DLE could modulate production of cytokines, including TNF-a, IL-6 [10] [11], and induce IFN-g secretion, driving immune response to a Th1 immune-regulatory response [12] [13].

Transferon™ is a human dialyzable leukocyte extract manufactured by National Polytechnic Institute (IPN), Mexico, at Good Manufacturing Practice (GMP) facilities. Transferon™ is registered by Mexican health authorities as a drug and is commercialized nationally. Although Transferon™ is a mixture of peptides, it has been demonstrated that there is a high batch-to-batch reproducibility in the chromatographic profile and also in the biological efficacy, demonstrated *in vitro* by up-regulation of IFN-g in a lymphocytic cell line (Jurkat clone E6-1) [1].

DLEs have been widely used since the 1970s due to their immune-regulatory functions for various clinical purposes [6] [14] [15]; to date, there are no current reports about the safety of Transferon™; thus, it was the aim of our study.

2. Methods

2.1. Patients

We included a total of 3844 patients in this study. The medical staff from the Clinical Immunology Service, Unit of External Services and Clinical Research (USEIC) at IPN, was responsible for clinical evaluation. Analysis was performed from January 2014 to November 2014, searching for clinical adverse events in patients who received oral formulation of Transferon™ (Pharma-ft, UDIMEB formerly Laboratorio de Investigación Científica, IPN, MEX) as adjuvant therapy in immune-mediated diseases.

Patients selected for the use of DLE as an adjuvant treatment were those with immune-related disease, and whose symptoms remained in spite of standard treatment for that specific disease. DLE dosing was indicated based on the guidelines suggested by Berrón-Pérez *et al.* [6]. Adverse events were evaluated in the population with the following selection criteria: all patients who were treated with DLE during the period of January 2014-November 2014 who took at least one dose of DLE, and followed dosing instructions as indicated. Pediatric patients were considered those younger than 11years. Patients signed an informed consent as part of running clinical protocols IC 12-001, IC 12-002, IC-12-003 designed to determine the safety of Transferon™. Patients aged between 8 and 17 years also gave their verbal assent to participate in these protocols. Adverse events were de-

fined in this study according to local law regulation in drug safety [16], and to the international regulation [17]. Serious adverse events were considered as any drug effect that results in death, life-threatening events, hospitalization, and disability; while nonserious adverse events were defined as drug related signs or symptoms that are tolerable, not life-threatening, sometimes needing additional treatment and/or require stopping the drug. The clinical terms used to describe each adverse event were based on terminology of the Medline Plus medical dictionary, from the National Institutes of Health [18]. As part of the national pharmacovigilance program, both serious and nonserious adverse events need to be reported to the federal authorities as stated by the Mexican Official Standard [16]. Adverse event surveillance was performed by the medical staff, and the pharmacovigilance unit helped to classify and report each event according to [16], defined in numeral 6.1.3. "Clinical Investigation Notification Method" of the Mexican Official Standard. All involved personnel were properly trained for reporting adverse events and knowledgeable in all relevant Mexican regulation.

2.2. Statistical Analysis

Statistical analyses were performed using the GraphPad Prism software, version 6.0f (San Diego, CA). Demographic variables were analyzed with descriptive statistics, and results are presented in tables and plots. In order to determine differences between groups, T test and X^2 were used, and a $p < 0.05$ was considered as statistically significant.

3. Results

3.1. Characteristics of Patients

From a total of 3844 patients that were included in this study, 42 patients of them developed 70 nonserious adverse events (AE). Incidence of nonserious adverse events was observed in 1.9% of patients treated with Transferon™ (MD 1.9%, IQR 1.7 - 2.0). AE were 2.8-times more frequently observed in female than in male patients ($p < 0.0001$); the mean age of adverse event presentation in adult patients was 47 ± 15 years old; while in children it was 5 ± 2.8 years old. AE were 3.2-times more frequent in adults than in children ($p = 0.0002$) (**Figure 1**). No serious AE were reported in patients treated with Transferon™.

3.2. Immune-Mediated Diseases and Adverse Events

Immune-mediated diseases in which adjuvant treatment with Transferon™ is indicated were classified into one of three types: Allergic Diseases, Infectious Diseases and Autoimmune Diseases. From a total of 42 patients that developed an AE, 41.4% were observed in patients with diagnosis of allergic diseases, 24.3% were observed in patients with diagnosis of autoimmune diseases, and 34.3% were observed in patients with diagnosis of infectious disease. Frequency of immune-mediated diseases and frequency of adverse events are depicted in **Table 1**.

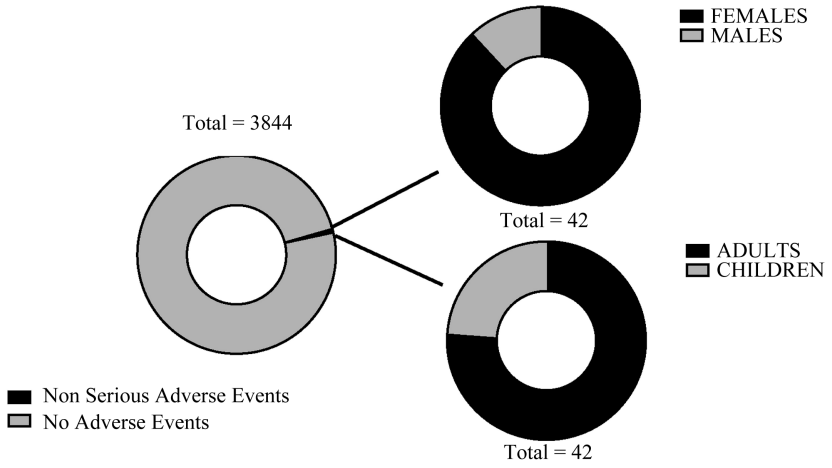

Figure 1. Distribution of adverse events and demographic data of patients treated with Transferon™.

Table 1. Immune-mediated diseases in which Transferon™ is indicated and adverse events observed.

Adverse events (AE) in different diseases	Patients	
	Number of patients with AE	Frequency of patients with AE (%)
Allergic diseases		
Allergic rhinitis	14	20
Asthma	11	15.6
Urticaria	2	2.9
Atopic dermatitis	2	2.9
Infectious diseases		
Upper respiratory infection	5	7.1
Infection by human papillomavirus	5	7.1
Herpes simplex virus infection	4	5.7
Infection by hepatitis C virus	2	2.9
Herpes zoster virus infection	1	1.4
Autoimmune diseases		
Rheumatoid arthritis	10	14.3
Systemic lupus erythematosus	5	7.1
Inflammatory bowel disease	3	4.3
Mixed connective tissue disease	2	2.9
Multiple sclerosis	2	2.9
Fibromyalgia	2	2.9

3.3. Adverse Events

The most common AE observed with DLE was headache in 15.7% of patients, followed by rash in 11.4%, increased disease-related symptomatology in 10%, rhinorrhea in 7.1%, cough in 5.7%, and fatigue in 5.7% of patients (**Figure 2**). The remaining adverse events in patients treated with DLE are described in **Table 2**.

3.4. Patterns of Onset and Resolution of Adverse Events

Transferon™ was administered in units, in a dose-reduction scheme, as suggested by Berrón-Pérez *et al*. [6]. One unit of Transferon™ is a standardized vial containing 2 mg of dialyzed peptides/5mL [1]. Total units received per patient were dependent of the diagnosis, and patients who developed AE were at different stages of treatment: 27.14% of patients were taking 1 U every day for the first week, 20% of patients were taking 2 U/week, 28.6% of patients were taking 1 U once a week, 2.3% of patients were taking 1 U every 10 days, and 21.3% of patients were taking 1 U every 2 weeks. We did not find a significant correlation between higher dosage and higher frequency of AE.

The majority of AE (63%) appeared between 1 - 4 days of treatment with Transferon™. AE lasted from 15 min to 14 days, and 77.1% of AE were resolved within the next 72 h after onset (**Figure 3**). In 32.9% of patients, Transferon™ was stopped because of adverse events; in 14.3% of patients, Transferon™ dosage was decreased after AE onset; and 2.86% of patients continued treatment with DLE without changes.

3.5. Drug Interactions

Although AE were more frequently observed in patients taking thyroid hormone or estrogen substitution, and/or

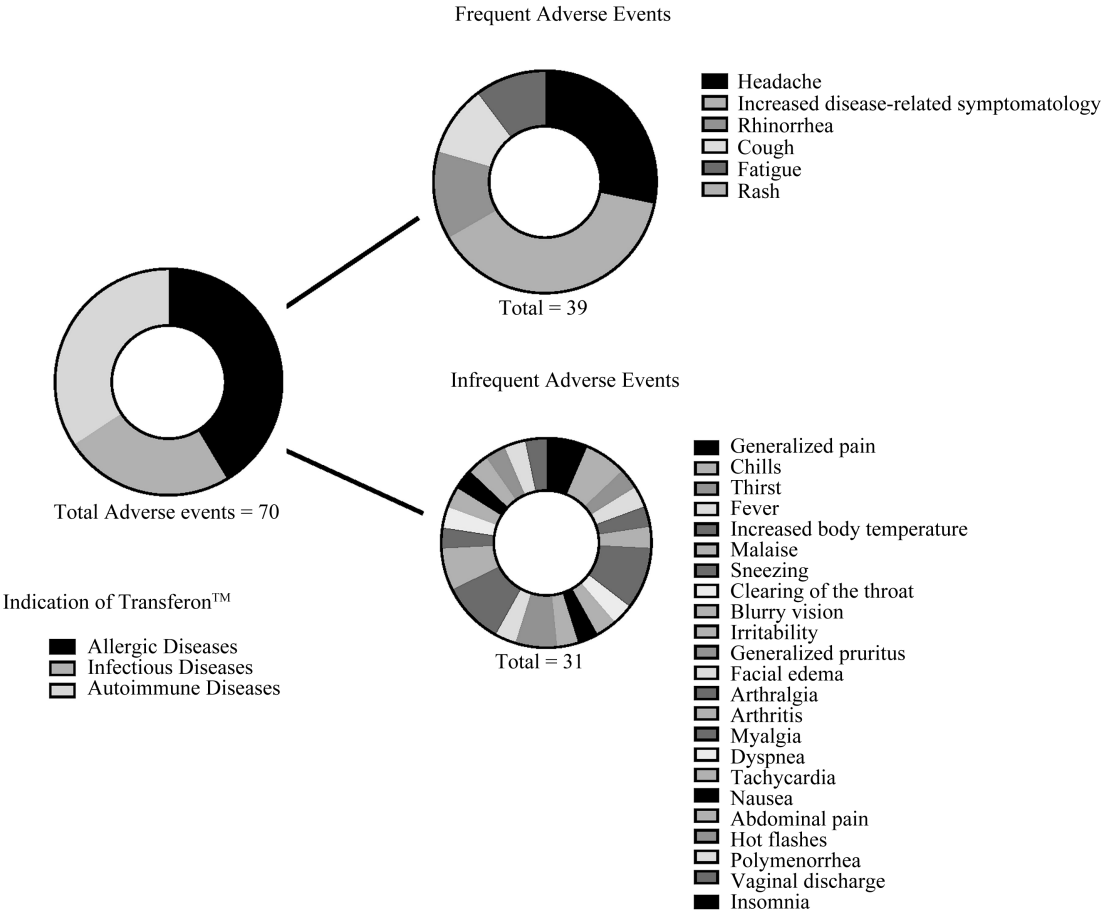

Figure 2. Distribution of type of adverse events in patients treated with Transferon™.

glucocorticoid therapy, no significant interactions between Transferon™ and other concomitant medication were identified.

4. Discussion

Dialyzable leukocyte extracts are heterogeneous mixtures of polar and hydrophilic peptides under 10 kDa, released after disruption of peripheral blood leukocytes from healthy donors [1]. DLE have been used to modulate immune response [1] [10]-[13] in patients suffering immune-mediated diseases [6] [14] [15]. Transferon™ is a human dialyzable leukocyte extract manufactured by National Polytechnic Institute (IPN), Mexico, at GMP facilities. The use of Transferon™ is widely extended in our country [6]; but despite their broad clinical use, to our knowledge no adverse events have been studied before.

In this work, we observed a low frequency of AE with the use of DLE. A significant adverse effect is usually considered as a reaction present in at least 2% of the studied population [19]. Of all included patients, only 1.9% of them developed adverse events. These results suggest that DLE is a safe and tolerable substance, but the unexpected low incidence of adverse events also opens the possibility of Transferon™-related adverse events may remain under-diagnosed.

Comparing our adverse event profile with adverse effects of glatiramer acetate (GA), a four peptide-based product with 5 - 9 kDa in size [19]-[21], we did not find similarities. GA is an injectable synthetic amino acid-based product with immune regulatory properties, reported incidence of adverse effects is at least 10%, mostly related to injection-site reaction. DLE is an oral peptide mixture lower than 10 kDa in size, and even though oral and injectable formulations cannot be fully compared, we expected to find some similar adverse effects between Transferon™ and GA. Nevertheless, some interesting patterns in adverse events presentation with the use of

Table 2. Adverse events identified in patients using Transferon™.

Type of clinical adverse event (AE)	Patients	
	Number of patients with AE	Frequency of patients with AE (%)
General symptoms		
Fatigue	4	5.71
Generalized pain	2	2.86
Chills	2	2.86
Thirst	1	1.43
Fever	1	1.43
Increased body temperature	1	1.43
Malaise	1	1.43
Ear, nose and throat		
Rhinorrhea	5	7.14
Cough	4	5.71
Sneezing	3	4.29
Clearing of the throat	1	1.43
Eyes		
Blurry vision	1	1.43
Neurologic		
Headache	11	15.71
Psychiatric		
Insomnia	1	1.43
Irritability	1	1.43
Skin		
Rash	8	11.43
Generalized pruritus	2	2.86
Facial edema	1	1.43
Bones, joints and muscles		
Arthralgia	3	4.26
Arthritis	2	2.86
Myalgia	1	1.43
Cardiopulmonary		
Dyspnea	1	1.43
Tachycardia	1	1.43
Gastrointestinal		
Nausea	1	1.43
Abdominal pain	1	1.43
Gynecology/Endocrine		
Hot flashes	1	1.43
Polymenorrhea	1	1.43
Vaginal discharge	1	1.43
Other		
Increased disease-related symptomatology	7	10
TOTAL	70	100

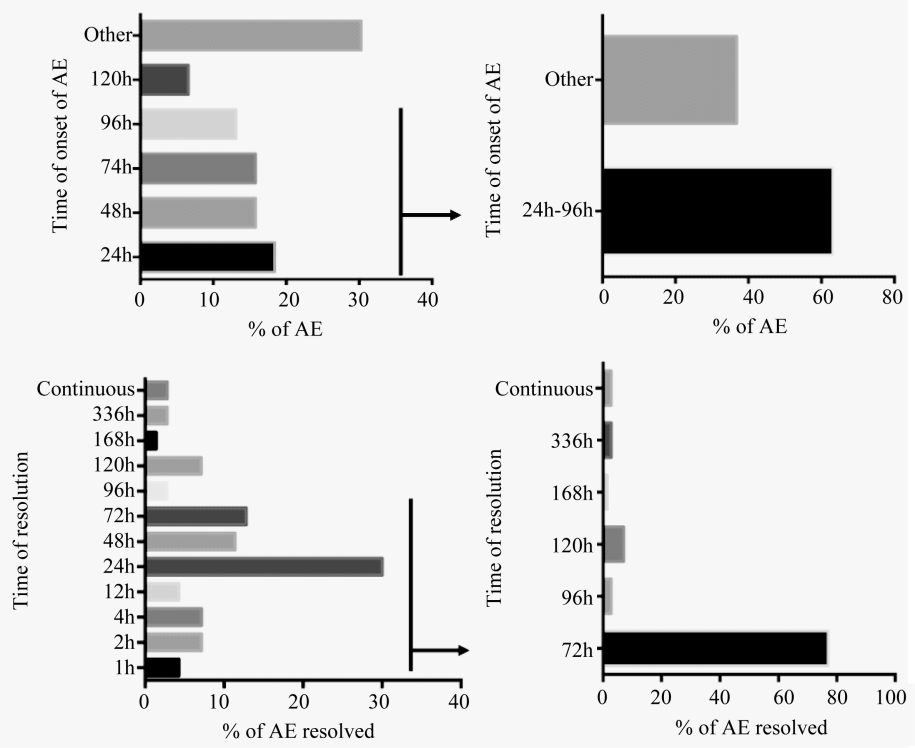

Figure 3. Time of onset and resolution of adverse events in patients treated with Transferon™.

Transferon™ are worth analyzing, *i.e.* AE were more frequent in females, and we detected 2 vulnerable age groups: ages 1 to 10, and 40 - 60 years old; this suggests that dosing should be reevaluated in order to reduce adverse events in both groups, and physicians need to increase clinical supervision to opportunely detect AE in children. It is unknown if hormonal factors may be involved in the female predominant adverse event profile showed in our study, but it is recognized that hormones may influence drug metabolism. Gender differences in adverse drug events have been observed before [22] [23], and factors other than hormonal effects such as body weight and differences in pharmacokinetics may be involved. In order to determine if hormonal factors are related in this pattern, it would be desirable to further study adverse event incidence in different female groups, such as before menarche and after menopause.

In this study we observed that most common AE were headache, followed by rash, increased disease-related symptomatology, rhinorrhea, cough and fatigue. In line with our results, the most common side effects of IFN-gamma include fever, chills, fatigue, myalgia, and headache [24]-[26], and it is well known that Transferon™ induces IFN-g *in vivo* [12] [13], and *in vitro* [1]. On the other hand, some DLE have been associated to an *in vitro* transient elevation of cAMP [8] [9], and increased concentrations of cAMP are related with headache [27]-[29], rhinorrhea [30] [31], and fatigue [32]-[34]. If Transferon™ is able to increase cAMP it is unknown, and needs further investigation. Importantly, no serious AE were observed in this study.

Limitations

The study population was heterogeneous, involving an extensive age group and patients presenting various different diseases as well as varied concomitant treatments for these diseases. Additional studies should be conducted in a controlled population. The low incidence of adverse events elevates the possibility that adverse events may be under-reported, and strengthening our pharmacovigilance protocols will aide in this matter. Finally, the lack of other adverse reaction reports associated to human DLE limits our possibility of comparison.

5. Conclusion

To our knowledge, no data on the adverse event profile of other DLEs have been published, and this study is an

adequate first step to describe adverse events associated with DLE and Transferon™; Transferon™ induced low frequency of nonserious adverse events during adjuvant treatment; however, further monitoring is advisable for different age and disease groups of patients.

Conflicts of Interest

S. E-P and M. P-T have been compensated for their work by UDIMEB, the producer of Transferon™. All other authors declare no conflict of interest.

Author Contributions

T.H.—performed clinical evaluation, analyzed and interpreted clinical immunological data, and wrote the paper; V.S.—trained medical staff in pharmacovigilance and developed pharmacovigilance procedures according to Mexican regulation. V.S., J.G.-C.; I.L.—collected clinical information, and analyzed data; E.C.-T., M.C.A., E.V., O.P., J.A.-B.—performed clinical-immunological evaluation of patients; A.E-G.—analyzed data, wrote paper; S.E.-P.—contributed with critical criticism of paper and wrote paper; M.P.-T. and M.C.J.-M.—designed the study, analyzed data, wrote paper and conducted research. A.E.-G. received a PhD scholarship from CONACyT number 164000.

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