

# The Rapidly Changing Landscape of Multiple Sclerosis Immunomodulatory Therapy: A Retrospective Chart Review in the United Arab Emirates

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## Abstract

The past 6 years have demonstrated a dramatic change in the landscape of immunomodulatory treatment for multiple sclerosis. Prior to 2010, there were no approved FDA oral immunomodulatory medications available. Since then, three new oral medications have been approved in addition to the newly approved alemtuzumab and ocrelizumab. This has dramatically changed the treatment options for MS patients. The older injectable agents – beta-interferons and glatiramer acetate are slowly being replaced. While data exists in the literature regarding the use of new medications in the west, there is little published data about the use of these new medications in the Middle East and, none, to our knowledge, in the United Arab Emirates (UAE). We conducted a retrospective chart review of four major government hospitals in Abu Dhabi looking at the types of MS in the Emirate, the use of different immunomodulatory treatment and the changes in prescribed medications between 2014 and 2016. A total of 328 people with MS were identified for the study. The proportion of participants receiving injections or infusions significantly ( $p=0.0013$ ) dropped from 53% (128) in 2014 to 42.7% (102) in 2016.

**Keywords:** Multiple sclerosis; United Arab Emirates (UAE); Immunomodulatory medication; Disease modifying therapy

## Introduction

Multiple Sclerosis (MS) is a chronic, progressive autoimmune demyelinating disorder affecting the central nervous system (CNS). Pathologically, the disease is characterized by destruction of myelinated axons and eventual progressive neurodegeneration [1]. Clinically, the course of the disease may vary, and MS has been divided into four phenotypic categories: primary progressive (PPMS), secondary progressive (SPMS), relapsing-remitting (RRMS), and clinically isolated syndrome (CIS). Diagnosis of MS can be challenging, with no definitive clinical or imaging tools. The McDonald criteria, most recently revised in 2010, rely on demonstration of characteristic T2 enhancing lesions on MRI with dissemination in both space and time [2]. Clinical symptoms of MS include bladder/bowel dysfunction, spasticity, fatigue, gait impairment, sensory disturbances and mood disorders.

Regardless of the type of MS, it is a chronic condition that places a significant economic and clinical burden on patients, their family members, and the healthcare system as a whole. As disability progresses in MS, the cost of care increases largely due to increased hospital admissions, need for home care and the cost of productivity loss [3].

Acute MS relapses are treated with high-dose corticosteroids for 3-5 days, which controls and shortens clinical relapse symptoms, but does not alter the natural progression of the disease. There is currently no cure for MS, and before 1993 no effective long-term treatments for RRMS were in existence. However, the past two decades have given rise to drastic changes in the treatment of RRMS. The first disease modifying therapies (DMTs) sought to dampen the immune response and control inflammation in the long term. Subcutaneous interferon beta-1b was approved in 1993 and was followed by several other subcutaneously administered medications: IFN $\beta$ -1a administered once weekly or three times weekly, glatiramer acetate (GA) and mitoxantrone [4]. Natalizumab, the first monoclonal antibody approved for the treatment of MS, was developed in 2004 and is administered via monthly infusions. Most recently on the market is alemtuzumab, approved as a third line therapy in 2013 and ocrelizumab just approved by the FDA in March 2017 [5].

The goal of MS treatment with DMTs is to reduce the frequency and severity of neurological disease progression, while simultaneously minimizing medication side effects and increasing medication adherence. Therefore, there was significant excitement over the development of the first oral DMT, fingolimod, introduced in 2010. This was followed by two others, teriflunomide and dimethyl fumarate (DMF) [5]. These newer oral medications allow patients to avoid injection-related side effects and improve the ease of medication administration. Additionally, these newer agents allow patients to avoid some of the widespread immune suppressant side effects seen with medications like cyclophosphamide and mitoxantrone [4].

Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) guidelines currently recommend the IFN-Bs, GA, teriflunomide and DMF as first line medications for RRMS, with fingolimod as an acceptable alternative in patients with needle phobia or contraindications to the previously listed medications. Fingolimod, natalizumab or alemtuzumab are recommended for patients with highly active disease (two or more disabling relapses in one year along with imaging findings) or as second line treatment [6,7]. Ocrelizumab, an anti CD20 monoclonal antibody, is the first medication approved to treat primary progressive multiple sclerosis. The aim of this study was to attempt to confirm the authors' clinical observations that more people with MS are choosing to change from injectable therapy to oral alternatives. The availability of medical records from four large government hospitals in Abu Dhabi made this an ideal situation to look at this subject in more detail.

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**Received** March 25, 2017; **Accepted** May 10, 2017; **Published** May 17, 2017

**Citation:** Schiess N, Holroyd KB, Aziz FAA, Huether K, Szolics M, et al. (2017) The Rapidly Changing Landscape of Multiple Sclerosis Immunomodulatory Therapy: A Retrospective Chart Review in the United Arab Emirates. J Mult Scler (Foster City) 4: 203. doi: [10.4172/2376-0389.1000203](https://doi.org/10.4172/2376-0389.1000203)

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## Methods

A retrospective chart review on people with MS followed at four large government hospitals in Abu Dhabi, UAE was conducted in 2014 by Schiess and was subsequently extended to include people with MS followed until the end of 2016 [8]. Tawam Hospital, Sheikh Khalifa Medical Centre (SKMC), Mafraq Hospital and Al Ain Hospital IRB approval was obtained and medical records searched between 2010 and 2016. Charts were reviewed for demographics, MS characteristics and current versus past immunomodulatory therapy. Primary progressive MS was excluded from the study. Subjects were divided into those taking injectable or infusion therapy versus oral DMTs and the McNemar test was applied to test the hypothesis that more people were changing from injectable or infusion medication to oral therapies.

## Results

A total of three hundred and twenty eight people with MS on DMTs were identified for the study and included 17 (5.18%) CIS, 280 (85.3%) RRMS and 31 (9.4%) SPMS. The average age was 36 years (SD: ± 10.6). Two hundred and twelve (64.6%) were female and one hundred sixteen (35.3%) were male giving a female/male ratio of 1.83. The majority (220, 67%) of subjects were Emirati citizens (Table 1).

In 2014, the top three medications prescribed included interferons (36.1%), fingolimod (30.1%) and natalizumab (8.5%). In 2016, the top three medications prescribed were fingolimod (27.3%), interferons (20.9%), dimethyl fumerate (11.7%) and natalizumab (10.6%). Within the two year period, 12.7% of patients were lost to follow up (Figure 1). Excluding those subjects who were lost to follow up, or newly diagnosed, the proportion of participants receiving injections or infusions significantly ( $p=0.0013$ ) dropped from 53% (128) in 2014 to 42.7% (102) in 2016 (n=239) (Table 2).

Of the 31 (9.4%) people with SPMS, more than half continued to take immunomodulatory medication despite the fact that none of the medications have been approved for SPMS. Natalizumab, fingolimod, dimethyl fumerate and interferons were the most commonly medications (Figure 2).

Characteristics	Frequency (n=328)	Percent (%)
<b>Age</b>		
0-14	1	0.3
15-24	42	12.8
25-34	108	32.9
35-44	113	34.4
45-54	44	13.4
55-64	19	5.7
65-69	1	0.3
<b>Sex</b>		
Female	212	64.6
Male	116	35.3
<b>Nationality</b>		
UAE	220	67
Non-UAE	108	33
<b>Type of MS</b>		
CIS	17	5.18
RRMS	280	85.3
SPMS	31	9.4

Table 1: Demographics and types of MS, Abu Dhabi, United Arab Emirates (2014-2016).

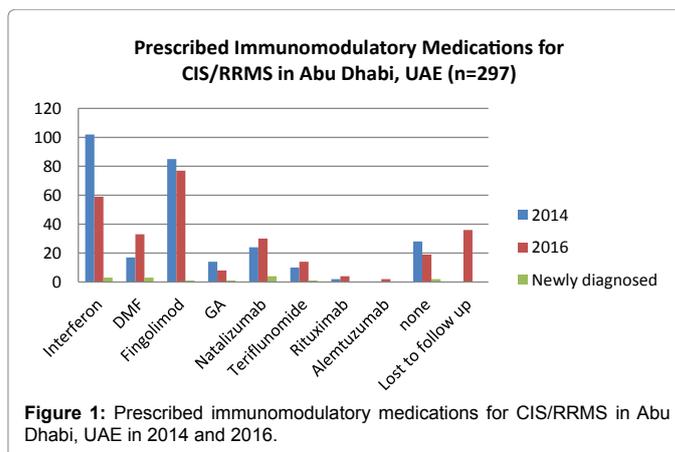


Figure 1: Prescribed immunomodulatory medications for CIS/RRMS in Abu Dhabi, UAE in 2014 and 2016.

m2014	m2016		Total
	Oral	Inj/Inf	
<b>Oral</b>	97 85.84	16 14.16	113 100.00
<b>Inj/Inf</b>	40 31.75	86 68.25	126 100.00
<b>Total</b>	137 57.32	102 42.68	239 100.00

Table 2: McNemar test was applied to test the hypothesis that more people would change from injectable or infusion medication to oral tablets ( $P=0.0013$ ).

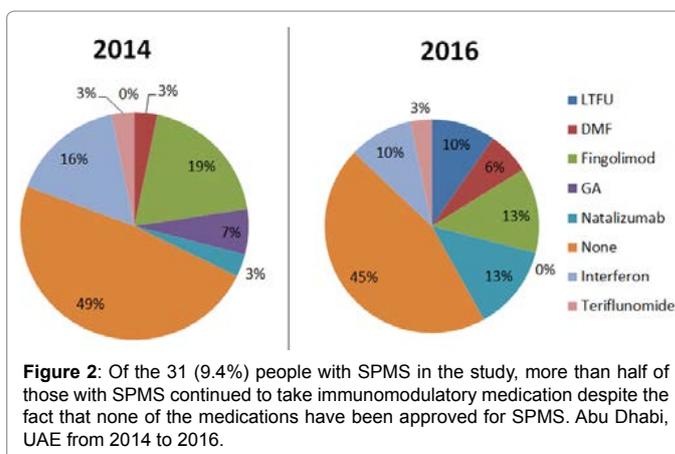


Figure 2: Of the 31 (9.4%) people with SPMS in the study, more than half of those with SPMS continued to take immunomodulatory medication despite the fact that none of the medications have been approved for SPMS. Abu Dhabi, UAE from 2014 to 2016.

## Discussion

The results of this study demonstrate that more clinicians and patients are opting to choose oral medication as opposed to the more traditional injectable therapies and that compliance appears to be increased with oral medications. Improving compliance to MS therapies is of utmost importance in clinical practice. In one study examining treatment adherence in RRMS patients over the course of 4.2 years, 46% of patients ceased treatment [9]. Studies estimate the highest rates of medication discontinuation within the first 6 months of treatment, with rates of discontinuation estimated between 9-20% [10,11]. Although rates of adherence are higher in patients enrolled in clinical trials, this is not a realistic treatment approach for all MS patients [12].

Although it is a reasonable hypothesis to assume that oral administration of medication will improve adherence, this has not yet been definitively proven in MS patients [12]. One 2015 study found that switching to fingolimod from an injectable medication led to fewer

relapses and greater treatment persistence [13]. Another study provided questionnaires to 156 MS patients and found that oral medications were preferred by 93% of patients. However, if pills had to be taken three times daily compared with a weekly or monthly injection, then injections were preferred by the majority of patients. Additionally, if dosing was held constant but pills were hypothesized to have side effects for 7 days a month and injections to have side effects only 2 days a month, injections were again preferred [14]. This demonstrates the difficult balance that must be struck between minimizing dosing frequency, side effects, and route of administration.

In order to improve adherence, clinicians need to better understand the wide variety of patient reasons for medication discontinuation. In a review by Patti et al. the authors discuss the main reasons for noncompliance with MS meds, including cognitive impairment such as depression, the onset of progressive MS, perceived lack of efficacy, and adverse events or side effects. A 2010 Middle East MS Advisory group consensus statement similarly recognized that two of the largest barriers to medication adherence in the Middle East are the use of injectable medications and unrealistic treatment expectations [15]. While some aspects of non-adherence may be out of the control of the treatment team, there are several techniques that can be used to improve adherence such as counseling patients extensively on the therapeutic benefit and risks of each medication, counseling patients on proper administration techniques and providing the patient with a support network such as self-help groups [12].

However, despite the excitement and changes in the field over the past 7 years, there still remains no magic bullet for RRMS. For example, fingolimod was shown to carry the risk of bradycardia and atrioventricular conduction block as well as macular edema, leading to regulations requiring increased monitoring before use [5,16]. Another oral medication, teriflunomide, was found to be teratogenic, limiting its use in pregnant and nursing women [17]. The excitement surrounding the development of natalizumab, the first humanized monoclonal antibody for the treatment of MS, was also tempered after the emergence of the rare but dangerous side effect of progressive multifocal leukoencephalopathy [5]. Additionally, the most recent antibody, alemtuzumab, was shown to be associated with significant secondary autoimmune conditions including thyroid disease and idiopathic thrombocytopenic purpura [18].

Although a possible increase in prevalence of MS in the Middle East has been noted [8,19], few studies on the safety, efficacy or use of MS medications have been conducted in the Middle East. Two studies examining the safety and efficacy of fingolimod in Kuwait [20] and Lebanon [21] have been published. However, no large-scale studies comparing oral and injectable medications or examining use of different MS medications have been performed. This paper examines the changing landscape of MS medication use in the UAE specifically and further research remains to be done on the efficacy and use of new MS medications in the Middle East MS population [19].

## Conclusion

The available options for treatment of MS have increased vastly in the past decade, but with these developments come new challenges. Clinicians now have the ability to choose between several oral, injectable or infusible medications for first and second line treatment of RRMS. Our data indicate that physicians and patients are choosing

oral medications more frequently in the UAE. Individualized decision making must be undertaken with heavy involvement of the patient, considering disease severity, side effect profile and route of administration. Continuing research and results of trials comparing the efficacy of newer medications against each other will be important in informing clinical treatment practices in the coming years.

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