Treatment Landscape of Multiple Sclerosis in Mosul: A Descriptive Cross-Sectional Study at Ibn-Sina Neurology Center

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that encompasses long-term usage of disease-modifying therapy (DMTs). In Mosul city, the availability, distribution, prescription patterns, and accessibility of such therapies is not fully explored.

Objective: To describe the current treatment landscape for MS patients at Mosul Neurology Center, including DMT usage patterns, common adverse effects reasons for therapy switching, age and gender distribution of patients, local drug availability and cost, patient satisfaction, and infrastructure conditions at the local biological therapy unit.

Methods: This descriptive cross-sectional study analyzed a random sample of 108 medical records drawn from a total cohort of 592 registered MS patients at Ibn-Sina Neurology Center. Collected data included age, gender, current DMT, prior treatment history, therapy switching, and relevant laboratory findings. The annual treatment cost of each drug class was assessed. Additionally, a structured patient questionnaire was performed in the biological therapy unit. Drug usage patterns were compared with UK and other global benchmarks.

Results: Eight drugs are currently used in the treatment spectrum of 592 registered MS patients. The pattern is coherent with international standards, but there is relatively high utilization of betaferon (21% of patients), and lack of other more useful options, like dimethyl fumarate. Fingolimod is associated with high rate of leukopenia, and betaferon is the most commonly discontinued drug. Treatment pattern is consistent with induction strategy, and analysis of annual cost shows that natalizumab is the most expensive, yet, valuable drug, followed by ocrelizumab and betaferon. Generally, 60% of patients receiving biological treatment are completely satisfied with their treatment.

Conclusion: The available DMTs landscape is fairly good, including the usage of multiple treatment options and continuous monitoring of adverse reactions. Yet, it can still be improved by reallocating resources from high-cost, lower-efficacy interferons to introducing oral agents like dimethyl fumarate.

Keywords: Multiple sclerosis, Disease modifying therapy, Treatment landscape**.**

المشهد العلاجي لمرض التصلب المتعدد في الموصل: دراسة مقطعية وصفية في مركز مستشفى ابن سينا لطب الاعصاب

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الخلاصة

الخلفية: التصلب المتعدد (MS) هو مرض التهابي مزمن يسبب إزالة الميالين في الجهاز العصبي المركزي، ويتطلب استخدامًا طويل الأمد للعلاج المعدل للمرض (DMTs). في مدينة الموصل، لم يتم استكشاف مدى توفر هذه العلاجات وتوزيعها وأنماط وصفها وسهولة الحصول عليها بشكل كامل.

الهدف: وصف المشهد العلاجي الحالي لمرضى التصلب المتعدد في مركز الموصل لطب الاعصاب، بما يشمل أنماط استخدام العلاجات المعدّلة للمرض، والآثار الجانبية الشائعة، وأسباب تغيير العلاج، وتوزيع المرضى حسب العمر والجنس، وتوفر الأدوية محليًا وتكلفتها، ورضا المرضى، وظروف البنية التحتية في وحدة العلاج البيولوجي المحلية.

الطريقة: تم إجراء دراسة مقطعية وصفية شملت عينة عشوائية من ١٠٨ سجلات طبية تم اختيارها من بين ٥٩٢ مريضًا مسجلًا في مركز ابن سينا للأعصاب. شملت البيانات المجمعة: العمر، الجنس، العلاج الحالي، تاريخ العلاجات السابقة، تغيير العلاج، والنتائج المخبرية ذات الصلة. تم تقييم التكلفة السنوية لكل فئة دوائية. كما أُجري استبيان منظم للمرضى في وحدة العلاج البيولوجي. وتمت مقارنة أنماط استخدام الأدوية مع المعايير البريطانية والعالمية.

النتائج: يُستخدم حاليًا ثمانية أدوية لعلاج ٥٩٢ مريضًا مسجلًا بالتصلب المتعدد. يتماشى النمط العلاجي مع المعايير الدولية، لكن هناك استخدام مرتفع نسبيًا لدواء بيتافيرون (٢١% من المرضى)، مع غياب خيارات علاجية أكثر فاعلية مثل ديميثيل فومارات. يرتبط فينجوليمود بمعدل مرتفع للإصابة بنقص الكريات البيضاء، ويُعد بيتافيرون الدواء الأكثر إيقافًا. يتوافق نمط العلاج مع استراتيجية الاستحثاث، وتبين من تحليل التكلفة السنوية أن ناتاليزوماب هو الدواء الأعلى تكلفة لكنه الأكثر قيمة، يليه أوكرليزوماب وبيتا فيرون. بشكل عام، فإن ٦٠% من المرضى الذين يتلقون علاجًا بيولوجيًا راضون تمامًا عن علاجهم.

الاستنتاج: المشهد الحالي للعلاجات المعدّلة للمرض جيد بشكل عام، ويتضمن استخدام خيارات علاجية متعددة مع مراقبة مستمرة للآثار الجانبية. ومع ذلك، يمكن تحسين علاج التصلب المتعدد بشكل أكبر من خلال اعادة توجيه الموارد بشكل أكثر فاعلية باتجاه ادوية اخرى مثل ثنائي ميثيل فوماريت.

الكلمات المفتاحية: التصلب المتعدد، العلاجات المعدّلة للمرض، المشهد العلاجي.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. It causes significant disability in affected patients, as it can affect virtually any part of the brain or spinal cord [1]. The hallmark of the disease is a process of demyelination of nerve sheaths leading to interruption of nerve conduction with the resulting partial or complete loss of function.

Both sensory and motor function could be affected, which could result in a very wide spectrum of possible symptoms including pain, tingling, numbness, weakness, disturbance of balance and coordination, and partial or complete loss of sphincter function[1,2].

If left untreated, the disease can be severely disabling, potentially leaving the patient wheelchair-bound due to significant lower limb weakness—an outcome that modern treatments aim to prevent [3,4].

The disease progression and clinical manifestations of MS are quite heterogeneous, with variable grades of severity, including an initial clinically isolated syndrome (CIS), to a relapsing–remitting form (RRMS) which could lead to a progressive development of permanent neurological dysfunction and disability (known as secondary progressive MS, SPMS).

Furthermore, some patients have a progressive course from the disease onset, recognized as primary progressive form (PPMS).

CIS and RRMS forms are classically characterized by active lesions of white matter demyelination, with heavy immunological involvement and activation.

The progressive forms, on the other hand, are generally characterized by inactive lesions, low inflammatory activity, and neurodegeneration[5,6].

The etiology of the disease is basically unknown, although several factors were characteristically linked to the disease activity and prevalence including vitamin D deficiency, genetic predisposition, sunlight exposure, geographic variations, stress, and possible viral infections. Yet, no single causative factor could be highlighted as a precise cause of the disease, which makes treatment of MS a very challenging task [2,7,8]. The pathophysiological mechanisms leading to the damage are still not very well understood. T cells seems to appear early in lesion development, and the disease is considered to be an autoimmune reaction, caused by autoreactive lymphocytes that initiate abnormal responses against CNS autoantigens. However, the precise nature of this reaction which, have not been precisely identified [9,10].

Interestingly, research has demonstrated that active MS lesions could be classified into four different immune-histopathological categories based on plaque topography, loss of certain myelin proteins, oligodendrocyte degeneration and evidence for complement and immunoglobulin deposition. These four categories can be referred to a “patterns of demyelination” [11]. Patterns I and II showed T cell and macrophage-associated demyelination with corresponding loss of all myelin proteins. Pattern II is specifically associated with immunoglobulin and complement deposited along myelin sheaths and present within macrophages, suggesting a classic mechanisms of humoral immunity.

Pattern III lesions, on the other hand are characterized by the presence of oligodendrocyte apoptosis and a specific loss of myelin associated glycoprotein located in distal oligodendrocyte processes. Its selective loss is thought to be a marker of metabolically stressed cells, leading to a dying oligodendrocytes and gliosis. Pattern IV lesions are rare and associated with non-apoptotic oligodendrocyte death around MS plaques. Pattern II is the most common, followed by patterns III, I and IV [9,10].

Currently, there are more than twenty FDA approved drugs available in the market, representing a wide variation in efficacy, mode of action, adverse effects, and mode of administration[11,12]. Going through detailed analysis of each drug category is beyond the scope of our research and the reader is referred to relevant detailed data available in literature. However, few notes on some relevant drugs are worth mentioning according to chronological order. The first FDA approved agent was interferon beta-1b (Betaferon) in 1993, administered subcutaneously every other day, it modulates the immune response by decreasing pro-inflammatory cytokines; common side effects include flu-like symptoms and injection-site reactions [13,14]. This was followed by interferon beta-1a (Avonex) in 1996, administered intramuscularly once weekly, and glatiramer acetate (Copaxone), a subcutaneous synthetic polypeptide that mimics myelin basic protein, inducing regulatory T cells; both share similar mild systemic and injection-site side effects. Interferon beta-1a (Rebif), was approved in 2002 for subcutaneous use three times per week [15,16]. Natalizumab (Tysabri) was approved in 2004 which is an intravenous monoclonal antibody blocking lymphocyte migration into the CNS, carrying a small but significant risk of progressive multifocal leukoencephalopathy (PML) [17-19].

The first oral DMT, fingolimod (Gilenya) was approved in 2010, is a sphingosine-1-phosphate receptor modulator sequestering lymphocytes in lymph nodes[13]. Bradycardia, lymphopenia, and infections are significant adverse effects. Teriflunomide (Aubagio) approved in 2012 is another oral agent; it inhibits pyrimidine synthesis and may cause hepatotoxicity and teratogenicity [14]. Dimethyl fumarate (Tecfidera), approved in 2013, activates the Nrf2 pathway and commonly causes flushing and gastrointestinal upset [13]. Alemtuzumab (Lemtrada) was approved in 2014; administered intravenously, it depletes CD52-positive lymphocytes and carries risks of autoimmune thyroid disease and infusion reactions.

Peginterferon beta-1a (Plegridy), was also approved in 2014; it extends the half-life of interferon for subcutaneous use [12].

Ocrelizumab (Ocrevus), was approved in 2017; it is a B-cell-depleting monoclonal antibody targeting CD20, given by infusion, and associated with infusion-related reactions and infections. Cladribine (Mavenclad), is an oral purine analog which was approved in 2019, it selectively targets lymphocytes, with lymphopenia as a major concern.

At the same time in 2019, siponimod (Mayzent), a selective S1P modulator for secondary progressive MS, was introduced, followed by ozanimod (Zeposia) in 2020, both given orally with similar cardiovascular and hepatic risks. Ofatumumab (Kesimpta), a subcutaneous anti-CD20 agent was approved in 2020, it causes B-cell depletion with injection-site reactions. On the other hand, ponesimod (Ponvory), was approved in 2021, is another oral agent similar to fingolimod. Most recently, ublituximab (Briumvi), an anti-CD20 monoclonal antibody for intravenous infusion, was approved in 2022, offering a new option with a favorable infusion schedule[12].

Additionally, several fumarate-based oral alternatives such as diroximel fumarate (Vumerity) and monomethyl fumarate (Bafiertam) have emerged, offering similar mechanisms to Tecfidera with potentially improved gastrointestinal tolerability. These agents represent a diverse group of mechanisms and routes, permitting individualized therapy selection, but also calling for careful consideration of safety profiles [12]. Rituximab (MabThera), a CD 20 depleting agent, is probably the most widely used drug outside the sphere of official FDA approval [20-22]. Nevertheless, as an off-label drug its efficacy is established and very well documented in medical literature, where in Sweden, for example more than 50% of MS patient receive it with favorable data supporting its safety and efficacy [23,24].

The pivotal efficacy data is variable from relatively low efficacy for interferons [23] (31%, 37%,33% for betaferon, avonex and rebif respectively). Teriflunomide also has a low efficacy of around 32-36%.

While other monoclonal antibodies are considered high to moderate efficacy drugs [23] (48-60%, 68%, 47% for fingolimod, natalizumab, and ocrelizumab respectively).

Currently, there are two different treatment trends of MS, the classic strategy is an escalation therapy, starting with a modestly effective, yet more safe, initial agent and switching to a more efficacious medication in cases of disease progression.

The second trend is induction therapy, starting with a high-efficacy drug and stepping back to lower efficacy options following a period of disease stability. Recently, there is an increasing evidence favoring the early initiation of high-efficacy DMTs, because this may have a beneficial long-term positive effect on disease progression which may have consequences for the shift of existing DMT usage landscape [15-17]. We therefore aimed to explore the nature and range of differences in MS DMTs utilization patterns and costs in Mosul.

SUBJECTS AND METHODS

The research was approved by the authorized committee at the Training and Development Center in Nineveh Health Directorate, and the study was conducted over the period of three months (1-June to 30-August 2025). Cross-sectional descriptive methodology was adopted. Three dimension were included in our study which was carried out at Ibn-Sina teaching hospital in Mosul.

This first dimension was focused on MS DMTs prescription patterns and landscape, where we had full access to medical records and statistical data of the specialized neurology unit at the hospital, which is the only place authorized to diagnose and treat MS in Mosul.

Hence all included patents' records and data were exclusively related to official MS diagnosis which was approved by specialized formal MS committee at the hospital. Out of 592 registered MS patient we collected a random sample of 108 medical records for further analysis which included, current therapy, age, gender, previous treatment lines, and registered laboratory analyses.

The second dimension was focused on the general infrastructure of the biological therapy unit at the hospital, where MS patients receive their biological treatment lines. Patients' impressions and satisfaction were assessed by an interviewer-led questionnaire, which was implemented along with direct observation and assessment by the research team.

The third dimension was focused on treatment cost of each therapeutic regimen where the relevant data were directly collected from the central medication storage at the hospital. This three-dimensional approach was very helpful to achieve a holistic and deep assessment of MS treatment environment at Mosul city.

Descriptive and analytic statistics were performed using SPSS software version 26.

The descriptive statistics included frequencies and percentages of DMTs. ANOVA was used to compare age and gender distribution among different drug groups.

RESULTS

Eight drugs were implemented in MS treatment landscape at Mosul neurology center. These were divided into first line therapies including betaferon, rebif, avonex, and teriflunomide; and second line including natalizumab, fingolimod, rituximab, and ocrelizumab. The total number and percentage of usage of each therapeutic option was registered according to our locally collected data at the neurology unit where 592 total MS cases were registered. Local percentages were contrasted with the percentages of each drug in UK and global records (obtained from the best possible estimates [25]) and are summarized in table (1). Figure (1) shows the percentage of DMTs in Mosul vs. UK and global benchmarks.

Table (1): The landscape of therapeutic options in Mosul in comparison with UK and global benchmarks.

No.	Drug	Number of patients in Mosul	Percentage in Mosul	Percentage in UK	Global percentage
1	**Betaferon**	128	21.62 %	2 %	6 %
2	**Avonex**	69	11.65 %	7 % (Combined)	11 % (Combined)
3	**Rebif**	47	7.93 %		
4	**Teriflunomide**	36	6.08 %	3 %	10 %
5	**Fingolimod**	48	8.1 %	12 %	13 %
6	**Natalizumab**	110	18.58 %	12 %	7%
7	**Rituximab**	105	17.37 %	Not used	5 %
8	**Ocrelizumab**	49	8.27 %	18 %	8 %
9	**Alemtuzumab**	Not used	0 %	7 %	1 %
10	**Cladribine (oral)**	Not used	0 %	2 %	2 %
11	**Dimethyl fumarate**	Not used	0 %	24 %	19 %
12	**Glatiramer acetate**	Not used	0 %	2 %	10 %
13	**Ofatumumab**	Not used	0 %	1 %	Not documented
14	**Diroximel fumarate**	Not used	0 %	3%	Not documented
15	**Siponimod**	Not used	0 %	5 %	1 %

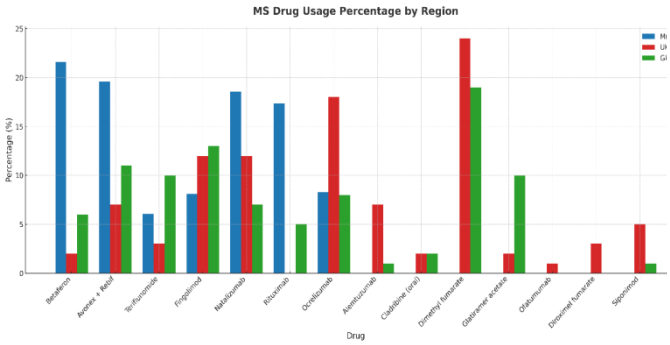

Figure (1) Percentage of DMTs in Mosul vs. UK and Global benchmarks

Gender distribution of our test sample of 108 medical record (66 females, 42 males, 61.11% and 38.89% respectively) was compared to the total number of 592 registered MS cases (382 females, 210 males, 64.5 %, 35.47 % respectively). Chi-square goodness-of-fit test = 0.55, p-value = 0.458 > 0.05 indicates that there is no statistically significant difference in gender distribution, and that our sample of 108 cases is a good representative of total MS group of 592 cases.

The mean age of patients at our test sample was 37.35 years (SD = 10.43), with a range of 13 to 64 years, and median of 38 years. Age distribution within the eight groups of our local therapeutic classes was compared to see whether there were any significant trends of prescription in relation to the age of the patients. For that reason, ANOVA test was used and showed that there were no statistically significant differences in age distribution between all eight treatment categories (F=1.805, p-value=0.094). This indicates that the selection of therapy seems to be unaffected by patient's age; an interesting and quite unexpected finding as patient's age is obviously linked to accumulation of neurological disability. This indicates that the local prescription pattern is at least partially leaning towards induction therapy, through prescribing more potent drugs early in the disease course [21]. Figure (2) shows the age distribution among our eight drug categories.

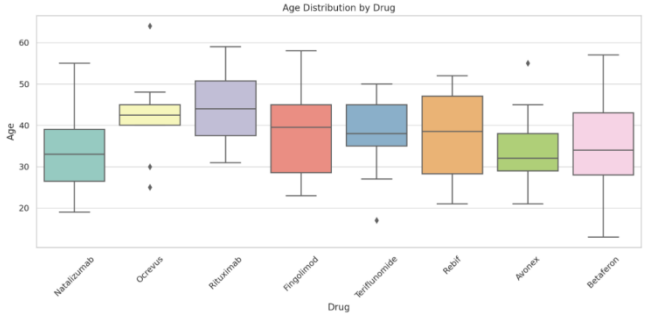

Figure (2): Age distribution among our eight drug categories.

On the same line, we compared the gender distribution within each drug category to the overall gender proportions of the study sample to identify potential treatment trends that may be influenced by gender-specific variations in drug usage. Chi-square: 3.904, and p-value: 0.79 indicate that there is no significant difference in gender distribution across the drug groups (p > 0.05). Concerning the number of previous treatments, 59.26 % patients (n=64) at our studied sample did not receive a previous MS treatment according to their medical records, while 30.56% (n=33), 6.48 % (n=7), 3.37% (n=4) had received one, two, and three previous drugs respectively. This indicates that most patients (nearly 60%) are treatment naïve, while around 40% had at least one prior treatment. Concerning this, the most commonly stopped drug was betaferon accounting to 45.2% (n=19) of the immediate previous therapy category, followed by Avonex (19%, n=8) natalizumab (19%, n=8), fingolimod (14.29%, n=6), and rebif (2.38%, n=1).

Apart from very few cases where the cause of drug switching was very clear in the medical record (pregnancy, hypersensitivity, or high JC virus titer), the vast majority of drug switching decisions appear to be caused by lack of efficacy, rather than adverse effects. An interesting finding was that although drug switching was generally from first line to second line, yet few cases (n=5) of new teriflunomide therapy (a first line drug) were preceded by betaferon (also a first line drug). This shows that there might be some realization and real clinical consideration regarding diversity MS immune mechanisms, where decision making could consider the possibility of individual variations in response to certain drug category regardless to overall efficacy profile. Concerning this, a follow-up longitudinal study is obviously highly recommended.

The most common laboratory abnormalities were high JC virus titer > 1.5 (5 cases in our study sample), and leukopenia (WBC count < 4,000 cells/µL) which was registered in 50% (n=5) of patients receiving fingolimod in our sample, in addition to 3 cases of high liver enzymes, 2 of them related to betaferon while the third was caused again by fingolimod. Although these findings were generally based on a relatively small number of patients which isn't optimal from a statistical standpoint, however, the coherence of the findings support their credibility. The annual cost of each drug category in Iraqi dinar (IQD) was calculated according to the official data which was collected from the central unit of medication storage at the hospital, after taking into account the price of individual drug multiplied by the number of required doses to treat one patient per year.

Natalizumab was the most expensive drug with an annual cost around 25 million IQD, followed by ocrelizumab and betaferon. Table (2).

Table (2): The estimated annual cost of MS treatment

No.	Drug	Treatment cost per unit in Iraqi dinar (IQD)	Annual treatment cost in Iraqi dinar (IQD)
1	**Avonex**	74,000	**3,848,000**
2	**Rebif**	29,000	**4,664,400**
3	**Betaferon**	52,000	**9,490,000**
4	**Teriflunomide**	3.029 per tablet	**1,105,585**
5	**Rituximab**	1,147,000	**2,294,000**
6	**Natalizumab**	2,047,000	**24,570,000**
7	**Fingolimod**	10,625 per tablet	**3,878,125**
8	**Ocrelizumab**	5,340,000	**10,680,000**

Finally, an interviewer-led patients' questionnaire was used to assess their overall satisfaction and suggestions. Both close and open ended questions were included in order to encourage patients to freely express their, demands, worries and views. Eighteen patients were interviewed (12 females and 6 males), and of these 15 were on natalizumab, 2 on rituximab and one on ocrelizumab. The replies showed that eight patients (44 %) were completely satisfied with their treatment plan, drug efficacy, and quality of life, without reporting any noticeable issues. Three patients 16.6 % were also satisfied, but expressed minor temporary adverse reaction related to their treatment. Adding this to the previous group makes a total of 60 % of patients did not express major concerns, and thus leaving us with 7 patients (39%) who expressed serious issues related to their long-lasting disability, or concerns about lack of treatment efficacy. At least two patients were anxious about the availability of rituximab doses. Surprisingly none of the interviewed patients expressed any concerns about the facilities of the hospital, and ward infrastructure. This side was assessed by the research team and it was obvious the biological treatment unit which is currently working side by side with the ward of general medicine would need a future upgrade to provide dedicated ward, beds, and dedicated medical staff.

DISCUSSION

The spectrum of currently available DMTs which includes four first-line, low efficacy drugs, and four second-line moderate/high efficacy therapy seems to provide a relatively good balance between efficacy (concerning protection from relapses) versus possible adverse effects. In this regard there was a good follow up of relevant routine blood profile results, liver function test, and other drug related specific tests like JC virus and varicella zoster immunity. The specialized MS committee and neurology team seem to be making very good array of decisions regarding drug distribution and DMT selection through leaning towards induction strategy [21], rather than escalation, which is a very strong trend of prescription pattern worldwide [16,17]. However, as we don't have accurate and detailed data about prescription landscape and drug use percentages in the past, we expect that it may need time, and a linear follow up study to assess the possible future benefits of the current prescription strategy, although overall global data suggests positive and promising results [16,17]. In comparing locally available DMTs with developed countries and worldwide, it is quite expected that not all drugs are currently locally available, and truth to be told, it is neither wise, nor practically feasible, to provide every single newly approved drug.

Taking in consideration the possible very high cost of some DMTs besides the utmost care which should be provided and implemented while using newly approved agents, and putting this within the frame of the current hospital resources, infrastructure, and the need for good financial balance, it seems that there is no urgent need for a major shift in the current DMTs landscape. However, this does not imply, on the other hand, that no revision is actually needed or suggested. In this regard one could note that the use of betaferon for nearly 21% of patients seems to be very high in comparison with global standards [25]. Taking in consideration the relatively high cost of this treatment line, it's low efficacy, and the availability of other interferes (Avonex and Rebif) which have the same mode of action, efficacy, and adverse effect profile, and yet less annual cost, it seems that redirection of resources towards other locally unavailable DMTs is probably needed. The only significant gap in the current treatment landscape is the lack of dimethyl fumarate (Tecfidera), which could be an excellent possible link between first and second line local DMTs. This drug was approved since 2013, and it's been in the market for more than ten years with good safety and efficacy profile, and availability of multiple generic brands[12].

The reason why dimethyl fumarate could make an excellent bridge between first and second line local DMTs, is that it has a significantly higher efficacy profile in comparison with interferons or teriflunomide (50% vs. 31% and 31% for teriflunomide and betaferon respectively), and yet a quite acceptable risk of common adverse effects, which include gastrointestinal upset and flushing [12], and without the troublesome, and possibly more dangerous, genuine physical reaction of other second line drugs, like figolimod induced lymphopenia, or natalizumab related JC virus for example. For this reason, it doesn't seem a mere coincidence that dimethyl fumarate is used by 24% of MS patients in the UK, and 19% globally [25].

The decision to use rituximab as a cost effective off-label MS therapy is heavily supported in medical literature [5,9,19,20]. It is well known that rituximab was successful during FDA regulation throughout phase two, but the trials were voluntarily halted by the drug developer who was working on ocrelizumab, another B cell depleting agent which has a very similar mode of action, but with a humanized superior molecular structure. Therefore, rituximab was not pushed to phase three and formal FDA approval by the developer who favored ocrelizumab.

Although this decision has its strong scientific merits, yet, financial considerations cannot be completely ruled out[19].

Concerning patients' impressions and satisfaction and taking in consideration the disabling nature of MS, it was expected that patients' needs were disease oriented, rather than issues concerning hospital environment or infrastructure. This again doesn't imply that there is no need for possible improvement in overall MS treatment facilities including better space, provision of a dedicated hospital ward and medical staff.

CONCLUSION

The current MS treatment landscape provides a relatively decent spectrum of first and second line options of DMTs, with good patient follow up. Induction therapy is a valid treatment option in which its effects will show up with time. With the availability of more than 20 FDA approved drugs, continuous revision and updating is essential. More than half of the patients were satisfied with their treatment plan, but significant number had major concerns in relation to drug efficacy and availability.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Author's Contribution

All authors contributed equally to the manuscript.

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