Organization Logo

# Simple Model of Graphite and its Applications in Superlattice

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Scanning probe microscopy investigations have extensively used graphite as a substrate due to its chemical inertness and ease of cleaving. The atomically flat surface of graphite has provided an ideal platform for surface scientists to deposit various kinds of materials of interest for imaging and examining. The natural graphite surface is also worthy of further understanding as it consists of a variety of defects [1], among which superlattice structure is reported to be found on graphite surfaces, and its origin is not yet completely understood [2]. It is of general interest and wide applicability to have a simplistic model for theoretical interpretation of scanning tunnelling microscope (STM) images of graphite, and even molecular dynamic simulations on graphite [3]. Here we describe a model of graphite which is easy to comprehend and simple to implement (fig.1 and fig.2). This model simulates the atomic density of graphite layers, which in turn correlates with the local density of states. The mechanism and construction of such a model is explained with all the necessary details which are not explicitly reported before. This model is applied in investigating the corrugation conservation phenomenon and rippling fringes of the superlattice which we observed on graphite [4]. The "odd-even" transition along the atomic rows of a superlattice is simulated (fig.3), and this result is discussed with reference to other reports in the literature [5]. A comparison is made with the result of Cee [6] about the validity of the moiré rotation pattern assumption.

**Fig.1** 1nm x 1nm area simulated with three-fold symmetry and triangular pattern of atomic lattice as observed by STM

**Fig.2** 20nm x 20nm superlattice area with rotation angle of 2.5 degree is simulated. The three-fold symmetry agrees with the observation under STM

**Fig.3** "Odd-even" transition along the atomic rows (squared region) is observed in this model of 5nm x 5nm superlattice area

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# The Safety and Efficacy of Natalizumab for Relapsing-Remitting Multiple Sclerosis-Hera General Hospital Experience

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## Introduction and Background

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system (CNS) and causing brain changes like inflammation, demyelination, and axonal damage hence brain atrophy.[1-8] Multiple Sclerosis (MS) is one of the most common inflammatory neurological disorders in young adults, with an estimated worldwide prevalence of 30.1 cases per 100,000 population. MS prevalence and incidence are increasing regionally and globally. Recent data from Saudi Arabia estimates the prevalence to be 40.40 cases per 100,000 (overall population) and 61.95 cases per 100,000 for Saudi nationals. .[1] Despite how MS represents a common cause of disability among young adults, its etiology remains mostly unknown.[2] Patients with RRMS have their symptoms worsen over time while they also experience deficits in motor skills and cognition.[1-2] Unfortunately, no cure for MS is available despite the use of different disease modifying therapies (DMTs) some of them are highly potent.[3].[3] Medications like Natalizumab is considered one of potent (DMT) indicated to treat highly active RRMS patients with reported reduced relapse rate by 68% and risk of sustained disability progression by 42% against placebo in pivotal study. While recent studies explained how Natalizumab represents an effective treatment for patients with RRMS, the current study aims to address the potential implications for clinical decision-making. More specifically, we sought to address the possible outcomes that resulted from patients with RRMS in Saudi Arabia who received natalizumab treatments and compare the outcomes with those of previous studies conducted in the Gulf countries as well as in other parts of the world.

**Comment [1]:** Missing reference

**Comment [2]:** Reference missing

**Comment [3]:** Only a cohort from Hera Hospital is being analyzed. Is it fair to say that this represents how patients are treated in Saudi Arabia in general?

**Key words :** relapsing remitting Multiple sclerosis,Ntalizumab,Safety,Efficacy

## Methods

We conducted a retrospective single-center observational study at Hera General Hospital, a 450-bed facility, in Makkah, Saudi Arabia. Neurology service is the most well-established and well-organized practice at Hera General Hospital where the MS clinic was established in 2004. Currently, the MS clinic has 460 active patients. Data collection started in October 2018 and was completed in January 2019. Accordingly, we collected data from 52 RRMS patients over 18 years of age who received Natalizumab for 24 months. The patients were diagnosed with RRMS according to the revised 2017 McDonald criteria. Each patient also has needed to receive current Natalizumab treatments for 24 months or more prior to inclusion. Escalated patients from different types of DMTs and Naive highly active patients were included in the study. Relapses, MRI findings and EDSS were assessed during 6 months before start of Natalizumab and at least twice over 24 months on Natalizumab.

Data collected from all MS patients included their demographic information like age and gender, presentation of clinical RRMS symptoms (e.g., disease course, duration, relapse rate, and EDSS score), the number of natalizumab treatments received, and adverse events that resulted from taking Natalizumab. The 52 RRMS patients received 4 weeks dosing regimen of Natalizumab infusions over 24 months. All patients had JCV serology tests performed on them before receiving infusions.

**Comment [4]:** At least 24 months?

**Comment [5]:** Repetitive

**Comment [6]:** No STRATIFY testing during treatment?

## Results

Demographic data indicated that 61.5% (n = 32) of the RRMS patients were female while 38.5% (n = 20) were male. The average duration of RRMS symptoms was 7.9 months and 88.5% (n = 45) of the patients experience relapse before receiving the natalizumab treatment. The average score EDSS score was 3.5 out of 5.5. Approximately 67.3% (n = 35) experienced DMTs before receiving the natalizumab treatment and 32.7% (n = 17) were unfamiliar with the medication. JCV serology tests indicated that 17.3% (n = 9) patients had JCV antibodies and 82.7% (n = 43) of the patients did not have the same antibodies. All data collection was anonymous and each patient was assured of confidentiality. The study was approved by the institutional review board (IRB) of Hera General Hospital.

The results at 24 months indicated that any discontinuation of natalizumab was due to a high JCV index. One RRMS died before the study was completed. However, the results did not indicate any reports of adverse events or side effects. The results indicated further that natalizumab is a safe drug with no infusion-related allergic reactions for 24 months and beyond. The formation of Gad+ or new T2 lesions decreased by 88.5%. Yet, 77% of the patients in the retrospective cohort were found to have relapsed. The overall results indicated that 48% of the patients showed stability in disease progression, 23% showed measurable improvements, and 23% showed worsening and escalating symptoms. Interestingly, 71.2% (n = 37) of the patients continued to use natalizumab after 24 months. After 24 months, 88.5% (n = 46) of the patients revealed no Gad+ or new T2 lesions. Only 11.5% (n = 6) of the patients presented new T2 lesions without relapse. Meanwhile, 48% (n = 25) of the patients had a stable EDSS score after 24 months while 23% (n = 12) of the patients had a worsening EDSS score and 28% (n = 15) had an improved score.

The results confirmed those presented in an earlier study comparing the impacts of natalizumab to delayed-release dimethyl fumarate.[5]. Here, we defined the latter as a therapeutic option for patients with RRMS previously treated with natalizumab who also required changes to the medication received. One major problem with the findings concerns how few studies present the indicators of favorable treatment outcomes for dimethyl fumarate. Another major problem concerns variations between clinical practices and sequencing protocols. While the results of the current study indicate the efficacy of natalizumab on patients with RRMS, the empirical findings of clinical trials performed in the future should present more precise details highlighting why some patients switch medications or discontinue them entirely. While clinical MS symptoms in Saudi Arabia continue to indicate high prevalence rates of the neurodegenerative disorder, the results of this single-center retrospective study have implications for understanding why some symptoms progress or decrease in their severity.[7] More importantly, future retrospective studies will need to involve researchers addressing how patients with RRMS who also receive natalizumab increase their overall functional mobility when Gad+ or T2 lesions decrease in size.

## Discussion

The importance of conducting observation studies resides in the need to obtain data from real clinical experiences and monitor safety concerns. Since this study focused on 52 RRMS patients who receive natalizumab treatments at a hospital in Saudi Arabia, the findings should ideally confirm what previous clinical researchers noted upon conducting long-term evaluations of safety and effectiveness.[16] Nevertheless, a larger sample size and the inclusion of another study site could produce more robust results by which clinicians make valid comparisons between empirical treatment outcomes. Data from a ten-year multinational prospective observational study on 6,148 patients with RRMS indicated that only a small percentage presented the risk of PML while 13.5% percent experienced serious adverse events from receiving natalizumab while slightly more than half of the patients discontinued treatment and almost one-third of the patients withdrew completely from the study[16] Meanwhile, an epidemiological survey on MS in the Arabian Gulf countries indicated that changes in the incidence and prevalence rates of RRMS often reflect the responses to natalizumab treatments.[4] The survey data indicated further that countries like Saudi Arabia have a high MS prevalence requiring greater public awareness throughout the Gulf region. However, more research on patient education is necessary to

**Comment [7]:** Will this be shown in a table and include mea range, etc.?

**Comment [8]:** I miss baseline MRI data and ARR.

**Comment [9]:** During what time period? (e.g. on year prior t starting NTZ?)

**Comment [10]:** EDSS scale goes up to 10

**Comment [11]:** What was the range of EDSS scores?

**Comment [12]:** Which prior DMTS were used?

**Comment [13]:** Prior to start NTZ? Or also measured during treatment? Will you be differentiating betwee different index levels?

**Comment [14]:** Assuming this was most common reason for discontinuation – what percentage of patients d/c'd due to high JCV index?

**Comment [15]:** The patient passed away without any noted reason? Do you mean that there no natalizumab-related AEs that were the cause death? Or is the second sentence a general statement for all adverse events for all patien

**Comment [16]:** Now you are looking beyond 24 months, but t analysis is based on data up to 24 months of treatment, correct?

**Comment [17]:** Baseline MRI data is not provided. Include thi baseline MRI data to prove this statement.

**Comment [18]:** What is the definition of a relapse? What is the ARR? Also at baseline.

**Comment [19]:** This is very high for natalizumab – please confirm.

**Comment [20]:** What about the other 6% not mentioned? Or does the 23% showing improvement need to 28% as mentioned in the last sentence of this paragraph?

**Comment [21]:** Which definitions were used for disease progression and improvement? 12 or 24-wee confirmed worsening/improvement?

**Comment [22]:**

**Comment [23]:**

**Comment [24]:**

**Comment [25]:**

**Comment [26]:**

**Comment [27]:**

**Comment [28]:**

**Comment [29]:** This paragraph belongs in the discussion

**Comment [30]:** ? Again, out of scope for this analysis.

**Comment [31]:**

**Comment [32]:**

provide more conclusive empirical findings on the long-term impacts of natalizumab.

To the concern of many physicians, the results of one five-year retrospective study on MS patients treated with natalizumab indicated higher brain volume loss within the first twelve months. Yet, the experiences of brain volume loss after 24 months of treatment remain largely unknown.[17] Small sample size is one reason for the lack of empirical data linking natalizumab to brain loss volume reside. The retrospective study reviewed changes in brain volume in only ten patients, nine of whom were women, with a mean age of 29 ±years, a median EDSS score of 2 ±15, and a mean disease duration of 6 ±5 years after 12, 24, 36, 48, and 60 months.[17] Most intriguing about this retrospective study is how the researchers accounted for reductions in brain volume at 24 months but could generalize their findings in terms of patient education.[4, 17] While the data suggested that brain volume loss decreased after 12 months of treatment, long-term follow-up studies highlighting the risk of brain atrophy in other patients cohorts is necessary.

Concerning gender, two studies addressed the potential risks of natalizumab treatments in pregnant women diagnosed with RRMS.[6, 18] In the first study, researchers analyzed the safety and impact of natalizumab on the disease course, pregnancy, and newborn outcomes of 11 women from the Austrian Multiple Sclerosis Treatment Registry (AMSTR) at eight weeks before the last menstrual period.[6] Each patient completed a questionnaire on pregnancy and newborn outcomes for up to 12 months after the postpartum period. While the researchers recorded 11 live births and one termination due to ectopic pregnancy, they also found that the termination of treatment occurred just 46 days after the last menstrual period. Three patients experienced symptom relapse during pregnancy and three more patients experience relapse in the postpartum period.[6] Accordingly, the first study presented results indicating that pregnant women exposed to natalizumab did not present a significantly increased risk of relapse. Concerns about disability during pregnancy and the postpartum period warranted further research in this regard. In the second study, researchers noted how some pregnant women in the United States (US) and the European Union (EU) should not breastfeed newborn children after receiving natalizumab treatments.[18] Study results also highlighted that women in the US diagnosed with RRMS should discontinue natalizumab treatments upon becoming pregnant and women in the EU should consider the potential risks of birth defects. For women in the EU, contraindications of treatment results during breastfeeding confirmed recommendations for discontinuing treatment.

More specific to the EU, the results of an extensive observational study conducted on 1,364 patients at 86 treatment centers throughout Spain indicated that 93% received prior DMTs for MS while the mean EDSS score decreased by 0.5 points from baseline and 14% discontinued the treatment.[19] Patients in this observational study presented more severe symptoms. However, the risk PML confirmed the results of previous studies identifying the potential risks of natalizumab treatment in some patients.[10, 13-14, 18] These results confirmed how some RRMS patients are at a ten-fold risk of developing PML and 20% risk of increasing their mortality rate.[2] Most of the risk factors for developing PML include an anti-JCV-positive, previous use of immunosuppressant medications, and the length of natalizumab treatment.[2, 15] Yet, an update to a consensus statement on natalizumab treatments that included new data on diagnostic procedures, patient monitoring, and PML noted how these risk factors should present a need for discontinuation.[15] Researchers should, therefore, consider categorizing PML risk factors according to the presence of anti-JCV-positive antibodies and not consider the contraindications associated with natalizumab treatments.[15, 18] In doing so, researchers will need to consider how the restrictive inclusion criteria of clinical trials may limit the relevance of findings in future observational studies. Researchers will likely need to rely on data from real clinical practice to produce more conclusive findings on the impacts of PML factors on different patient cohorts receiving natalizumab treatments. Comparisons between different study sites in Saudi Arabia may also produce more robust statistical findings with implications for improving practice.

The findings of this study also present implications for distinguishing between the various impacts of immunomodulation and immunosuppressant drugs. For patients with RRMS, immunomodulation drugs tend to interact with different areas of the immune system. By comparison, immunosuppressant drugs limit how the body responds to infections agents or vaccinations. However, researchers have yet to understand the full impacts of immunomodulation drugs on the CNS.[20] Professional bodies like the World Health Organization (WHO) Collaborating Center for Drug Statistics provide researchers with a

**Comment [33]:**
Patient education focused on…? I don't understand how patient education is linked to long term impacts of natalizumab. What type long term impact? Safety, efficacy, employment? This is not clear.

**Comment [34]:**
This reference describes the higher brain volume loss in the first 12 months as "pseudo atrophy", which is linked to a reduction of brai inflammation when natalizumab is initiated. T analysis of atrophy data from the AFFIRM (Miller et al, 2007) describe the same thing. T way this is written here it appears that natalizumab treatment is the cause of this atrophy, not the pseudo-atrophy.
Also, there is no focus on brain atrophy in this KSA analysis. How is this part of the discussi linked to the analysis performed?

**Comment [35]:**
Given the present study does not address bra volume loss, why are we discussing brain volume loss here?

**Comment [36]:**
? I don't understand what patient education h to do with this – translation issue?

**Comment [37]:**
Why not refer to the outcomes in the Tysabri pregnancy registry with 369 MS patients on NTZ included in the analysis? Friend S et al. BMC Neurol. 2016;16:150

**Comment [38]:**
The present analysis does not focus on pregnancy so why are we addressing this top in the discussion?

**Comment [39]:**
Natalizumab treatment

**Comment [40]:**
Symptoms of MS, meaning a higher severity MS at baseline?

**Comment [41]:**
This is referencing a different article based or the experience in Saudi Arabia. It's not clear that outcomes are being compared between t Spanish observational trial and the experienc in Saudi Arabia.

**Comment [42]:**
These are the known risk factors for the development of PML in natalizumab treated patients.

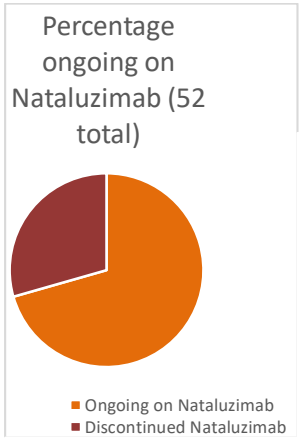
**Comment [43]:**
What do you mean with "contraindications"? I you mean not to consider the use of immunosuppressants prior to natalizumab treatment when considering PML risk?

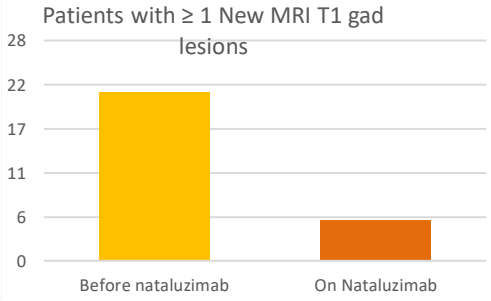
**Comment [44]:**
Do you mean to go beyond the currently know risk factors?

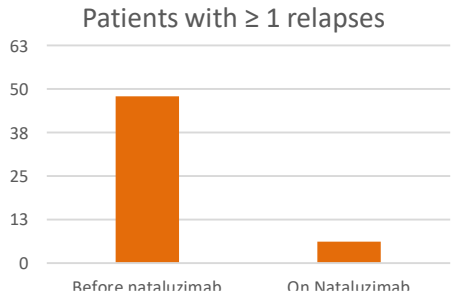
**Comment [45]:**
How was this proven in the analysis done? I d not see any data based on a comparison with other DMTs?

schematic framework for classifying immunomodulation and immunosuppressant drugs. Yet, the continuous use of immunosuppressant medications like natalizumab presents functional consequences for how patients with RRMS benefit from treatment. Patients may receive some benefits from fingolimod and dimethyl fumarate treatments.[2, 5, 8-10] Still, more research on how patients at Hera General Hospital benefit from different immunomodulation and immunosuppressant drugs should receive ongoing attention when future retrospective studies include comparisons between cohorts.

As for the presence of Gad+ or T2 lesions, research on the best practices for treating RRMS indicates that patients who had one medically documented relapse within 12 months before participating in a retrospective study will likely decrease their EDSS score consistent to natalizumab or a placebo.[12] Accordingly, patients receiving natalizumab treatments will also present reduced inflammation characteristics and reduced disability progression after 12 months. MRI lesion activity also tends to decrease after 12 months when patients receive natalizumab. Concerns about PML risk aside, current observational studies correspond to antibody development when the kinetics of natalizumab present a strong association with late hypersensitivity reactions.[5, 8, 12-14] However, more follow-up studies are necessary so that researchers may account for treatment impacts beyond 24 months.[4, 17] If follow-up studies produce results like those highlighted in the current single-center retrospective study, clinicians in Saudi Arabia can more accurately account for the long-term impacts of natalizumab when its safety profile remains well-established.[16] Despite how the long-term safety profile of drugs like alemtuzumab present concerns about the emergence of adverse events like severe neutropenia, pulmonary bleeding, myocardial infarction, and stroke, that for natalizumab illustrates the potential to produce more promising results in future studies. Even so, increased patient education will encourage individuals with RRMS to consider their options based on how the currently available treatments leave varying impacts on short- and long-term health outcomes.




## Conclusions

**Comment [46]:** Missing reference

**Comment [47]:** I miss mention of EID and current research being done to mitigate PML risk in the future.

The study at Hera General Hospital in Saudi Arabia provides further support for the efficacy of natalizumab in the clinical practice setting. While the study could have benefited from having a larger sample size and the inclusion of patients from at last one more site, the decrease in relapse rate and overall improvement following natalizumab treatment was similar to previous observational studies conducted in Saudi Arabia and other parts of the world. From the perspectives of both physicians and patients, natalizumab is a reliable therapy for the management of RRMS symptoms in the selected study population. Natalizumab remains the most commonly used medication for patients fulfilling the inclusion criteria. However, some patients included in future retrospective or observational studies may present risk factors that will require the discontinuation of natalizumab treatment. While most patients with RRMS respond favorably to natalizumab, the risk of PML will continue to present some cause for concern when cases present the likelihood of experiencing adverse events. Concerns about PML aside, the long-term safety profile of natalizumab indicates that the current protocols for treatment RRMS in Saudi Arabia could involve clinicians educating patients about the differences between immunomodulation and immunosuppressant drug therapies. Similarly, patient education delivered by clinicians could potentially increase rates of medication adherence when fingolimod and dimethyl fumarate do not produce the anticipated treatment outcomes.

**Comment [48]:**
Approved label indication

**Comment [49]:**
Adherence to natalizumab treatment?

~~DISCLOUSURE~~

~~The authors disclose that BIOLOGIX company support the publication of this article~~

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