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Assessment and characteristics of Erenumab therapy on migraine management

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ABSTRACT

Background: Migraine is one of the neurological diseases that have a negative impact on subjects' productivity and daily activity of patients. Introducing monoclonal antibodies as a valuable option for resolving the persistent problem of migraine is still under investigation. The current study aimed to evaluate the efficacy and safety profile related to Erenumab.

Methods: A prospective study for clinical data collection and analysis from recruited therapy-refractory migraine subjects were carried through 6 months for each subject. All subjects received Erenumab 70 mg monthly. Each patient provided the clinical data monthly starting from 0 months and for the next 6 months. Migraine disability assessment (MIDAS) questionnaire was used for evaluation of the Erenumab efficacy every 3 months. In addition, data regarding adverse effects, migraine triggers, and the impact of previous COVID-19 on migraine severity were collected and analyzed.

Results: Ninety subjects were recruited in the study. Erenumab injections resulted in a significant ($p < 0.001$) reduction in MIDAS score in the 3rd month compared with baseline, also this significance was continuous in the 6th month. In contrast, there was no significant difference in the 6th month compared with the 3rd. Previously infected COVID-19 subjects showed a higher severity of migraine attacks compared with non-infected subjects. Skin redness and local pain were the most common adverse effects 63.3%, 47.77% respectively associated with Erenumab.

Conclusion: Using Erenumab therapy showed a great beneficial impact regarding the reduction of migraine-related disabilities. COVID-19 was related to the increased severity of migraine attacks.

1. Introduction

Headaches are one of the most common neurologic illnesses in the world. Around 30 % of adults between the ages of 18 and 65 suffer from headache disorders, with migraine accounting for another 30 percent (Mi et al., 2020). In the United States, nearly 15% of persons aged 18 and higher suffer from migraines (Jain et al., 2018). Migraine is a recurrent headache illness in which each pain episode lasts 4–72 h. The pain is usually pulsing, moderate to severe, and unilateral. All of these symptoms, including nausea and/or vomiting, as well as photophobia and phonophobia, are prevalent. (Arnold, 2018). Migraine can be divided into episodic and chronic migraines based on the severity and frequency of headache attacks. The term "episodic migraine" refers to that consists of individual attacks of migraine, but when these merge into continuing headaches for at least 15 consecutive days each month, with at least eight recognizable migraine attacks within those 15 days, current practice terms the situation chronic migraine, episodic migraine may progress to chronic migraine (Irimia et al., 2021). According to the 2016 Global Burden of Disease survey, migraine is the second most common cause of years lived with disability worldwide(Feigin et al., 2019).

It is estimated that 37 million people in the United States suffer from migraines, which can be debilitating (Shipley, 2020). In recent years, the treatment of migraine has undergone a substantial transformation as a result of the introduction of innovative biolog-

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ics. The use of preventative drugs for chronic or episodic migraine has traditionally required the use of medication that was created for other conditions but has been demonstrated to be unsuccessful in the treatment of chronic or episodic migraine (Grazzi et al., 2017). The discovery of new biologics that precisely target a molecule which is released from nerve fibers running along meningeal and cerebral arteries and blood vessels (Edvinsson et al., 1987; Meßlinger et al., 1993) known as calcitonin gene-related peptide (CGRP), which is implicated in the pathogenesis of migraine, has changed the landscape of migraine treatment(Shipley, 2020). These medications, which work by suppressing the activation of the CGRP receptor, can considerably reduce the number of headache days each month as well as the need for a variety of medications (de Vries et al., 2020).

The current study aimed at determining the efficacy and safety concerns related to the use of Erenumab and assessment of different aspects related to migraine. In addition, determining the impact of previous COVID-19 illness on migraine attacks.

2. Methods

The current study is a prospective analysis that recruited subjects suffering from migraines aged 18 years and older. The study was approved by the local hospital ethical committee (Fayoum University). All subjects included in the study were diagnosed with migraine 1 year at least, suffering from at least 4 migraine days monthly, and were eligible to receive Erenumab injections. Subjects were excluded from the study if they were pregnant, recently diagnosed, had a contraindication for using Erenumab.

The recruited subjects received Erenumab 70 mg once per month for 6 months. Each subject undergoes a data collection section monthly from the baseline till the end of 6 months. At baseline (0 months), all recruited subjects provided data regarding their migraine and medication status through the previous 3 months. Data collected at the first session were demographic data (age, gender, weight, and height) type of migraine prophylactic medications, caused of shifting to Erenumab, history of migraine (years), and migraine disability assessment (MIDAS) questionnaire. For the next sessions, subjects were asked to provide the adverse effects that were related to Erenumab use, the effect of previous illness with COVID-19 on the frequency of migraine attacks before starting the current treatment course (basleine).

MIDAS score was calculated according to the total number summed from answering and scoring questions related to the number of days that migraine attacks prevent the subjects from attending the work or school, days of reduced work productivity (50%) of the subject, days in which subject could not do the traditional household work, days of reduced household productivity (50%) of the subject, number of days in which subjects miss family, social or leisure activities. The MIDAS score was generated from the sum of all days for the subject during the previous three months. In addition to previous data, collecting data regarding the common triggers that stimulate their migraine attack was recorded for each subject.

2.1. Statistical analysis

All numerical data were expressed as mean ± SD or number (percent). Results were compared statistically before and after receiving the Erenumab therapy, also the comparison between 0, 3, 6 months MIDAS score was performed. The Wilcoxen and McNemare tests were used for the analysis of data. Data were analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Response surface plot was used to express the relation between 2 factors with a single response.

3. Results

Ninety subjects were included in the study and received Erenumab 70 mg for 6 months, their demographic and baseline data were expressed in Table 1. MIDAS score for the first 3 and next 3 months was reported in Table 2.

There was no significant difference regarding the value of MIDAS for subjects who received prophylactic therapy compared with those who did not receive any therapy before Erenumab.

Regarding the efficacy of Erenumab in reducing migraine attacks and its related negative impact, Erenumab showed a significant ($P < 0.001$) reduction in MIDAS score after 3 months of starting the therapy. Besides, there was no significant difference regarding MIDAS scores in the third and sixth months.

The increased severity was noted to be significantly ($P < 0.05$) higher with elder subjects as shown by Fig. 1.

There was no significant difference regarding the MIDAS score at 0 months for those with a long or short history of migraines. However, the severity of migraine decreased with time for adults' subjects, as the history of migraine was longer the severity was lower, while the opposite was true regarding females as shown by Fig. 2.

The frequency of migraine attacks was higher with the COVID-19 subject compared to non-covid-19 subjects for the baseline evaluation of all subjects as shown in Fig. 3.

Using Erenumab resulted in a significant ($P < 0.001$) reduction of topiramate and shifting to traditional non-steroidal anti-inflammatory drugs (NSAIDs), percent of subjects using topiramate before starting Erenumab therapy was 87.77% that reduced to 22.2% after receiving Erenumab injections. In addition, subjects wear able to discontinue using amitriptyline after 3 months (n = 6) and 6 months (n = 3) from starting Erenumab therapy. Participant continued to use other medications with Erenumab therapy such as triptan, NSAIDs, and paracetamol as shown in Table 2.

Regarding the safety concerns of Erenumab therapy, participating subjects reported that skin redness and local pain were the

Table 1
Demographic and baseline data.

Age ± SD (years)	39 ± 7.09
Gender (n (%))	Female (n = 60 (66.7%) & Male (n = 30 (33.3%))
Weight ± SD (Kg)	79.18 ± 12.24
Height ± SD (cm)	166.24 ± 7.16
Erenumab dose (mg)	70 mg
Number of received Erenumab doses	6 doses (once per month)
History of Migraine ± SD (years)	13.36 ± 4.65
Migraine triggers (n (%))	Neck pain (43 (47.8%))Sunlight (hot weather) (38 (42.2%))Humidity (31 (34.4%))smart phones (27 (30%))Sinusitis (35 (38.9%))Noise (36 (40%))
Patient receiving prophylactic medication (n)	Yes (58) & No (32)
Topiramate (n (%))	79 (87.8%)
Amitriptyline (n (%))	9 (10%)
Cinnarizine (n (%))	7 (7.8%)
Duration of using prophylactic therapy ± SD (year)	3 ± 1.41
Causes of discontinuing prophylactic therapy (n (%))	Not effective + Adverse effects = 19 (21.1%) Not effective only = 19 (21.1%) Adverse effects only = 2 (2.2%) Contraindications = 5 (5.5%)
Subjects previously diagnosed with COVID-19 (n (%))	53 (58.9%)

Table 2
Characterization of patients at baseline, 3 months, and 6 months after initiation of Erenumab.

	Baseline (prophylactic therapy)	3 months after Erenumab	6 months after Erenumab
MIDAS (Mean ± SD)	38.90 ± 11.49	14.31 ± 6.4	13.08 ± 6.29
Severe Migraine Attacks per month	13.49 ± 4.38	4.67 ± 2.26	4.32 ± 2.17
Add-on medications	Triptan + Ergotamine n = 30 (33.3%) Triptan alone n = 56 (62.2%)	Triptan n = 20 (22.2%) Paracetamol n = 70 (77.8%) ketorolac + paracetamol n = 10 (11.1%) triptnan + paracetamol n = 8 (8.9%)	

most common adverse effects 63.3%, 47.77% respectively, while 31.1% reported constipation to be the adverse effect.

The most common triggers that were reported to stimulate migraine attacks were Sinusitis, neck pain, sunlight (hot weather) as shown by Fig. 4.

4. Discussion

Regarding the efficacy of Erenumab in reducing migraine attacks and its related negative impact, Erenumab showed a significant reduction in MIDAS score after 3 months of starting the therapy. Besides, there was no significant difference regarding MIDAS score in the third and sixth months. This was consistent with Russo et al. (Russo et al., 2020) demonstrated throughout 6 months, the efficacy and safety of Erenumab in a sample of 70 chronic migraine patients who had failed at least four migraine, preventive drug classes. More specifically, after 3rd administration of monthly erenumab 70 mg s.c., 70% of patients considered "responders" (e.g., a 30% reduction in headache days/month) and continued on monthly erenumab 70 mg s.c., while 30% considered "non-responders" (e.g., a 30% reduction in headache days/month) and switched to monthly erenumab 140 mg s.c. After the subsequent 3rd monthly administrations of erenumab 140 mg s.c., 29% were classified as "responders." After the third monthly injection of erenumab 70 mg s.c., 53 percent and 18 percent of patients reported a 50% or a 75% reduction in headache days per month, respectively. After the sixth monthly delivery of erenumab (70 mg s.c. or 140 mg s.c.), 70% and 26% of patients reported a 50% or a 75% reduction in monthly headache days, respectively, compared to baseline.

In addition, the ARISE study in episodic migraine patients revealed a 2.9-day reduction in monthly migraine days compared to 1.8-days for placebo, as well as a 50% or greater reduction in monthly migraine days from baseline in 39.7% of patients treated with monthly erenumab administration compared to 29.5 percent of the placebo group (Dodick et al., 2018).

In a cohort of episodic migraine patients, the STRIVE research found a reduction in monthly migraine days of 3.2 in the 70-mg erenumab group and 3.7 in the 140-mg erenumab group, compared to 1.8 days with placebo. Furthermore, 43.3 percent of patients in the 70-mg erenumab group and 50.0 percent of patients in the 140-mg erenumab group experienced a 50% reduction in the mean number of migraine days per month, compared to 26.6 percent in the placebo group. (Goadsby et al., 2017).

The efficacy and safety of monthly erenumab administration were also observed in the LIBERTY study, in a group of episodic migraine patients who had failed two to four previous preventive treatments, with at least 50% reduction in monthly migraine days in the 30 percent of patients after the third monthly erenumab administration, compared to 14% in the placebo group. (Reuter et al., 2018). Altogether, many trials (Tepper et al., 2017; Barbanti et al., 2019; Lattanzi et al., 2019) found the efficacy and safety of erenumab in episodic migraine patients who have had

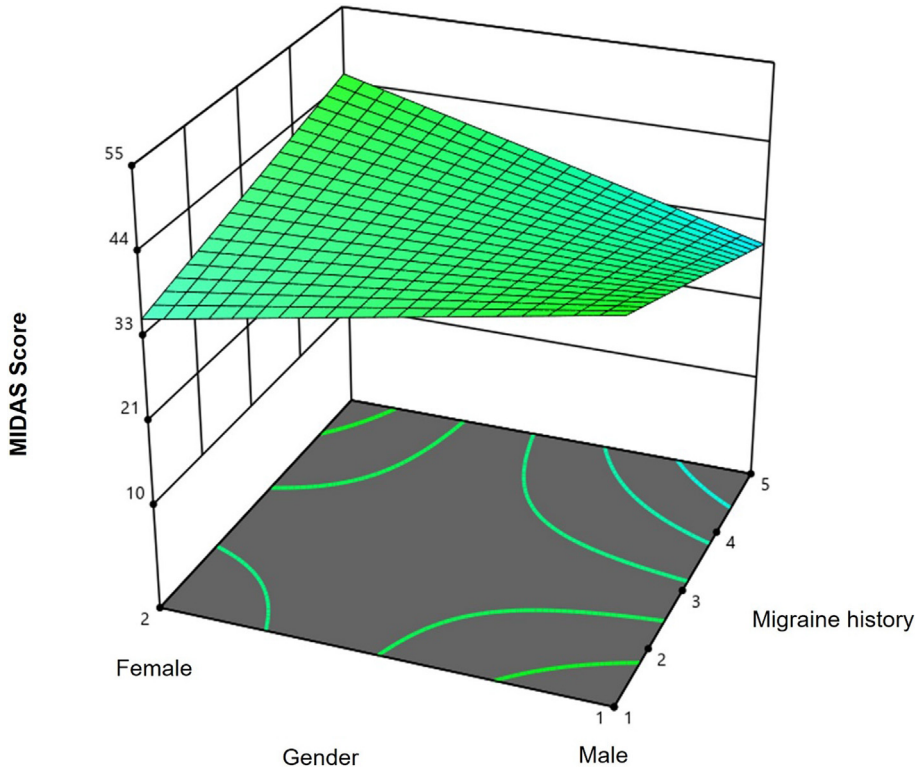

Fig. 1. Response surface plot showing the effect of age and gender on the severity of migraine attacks.

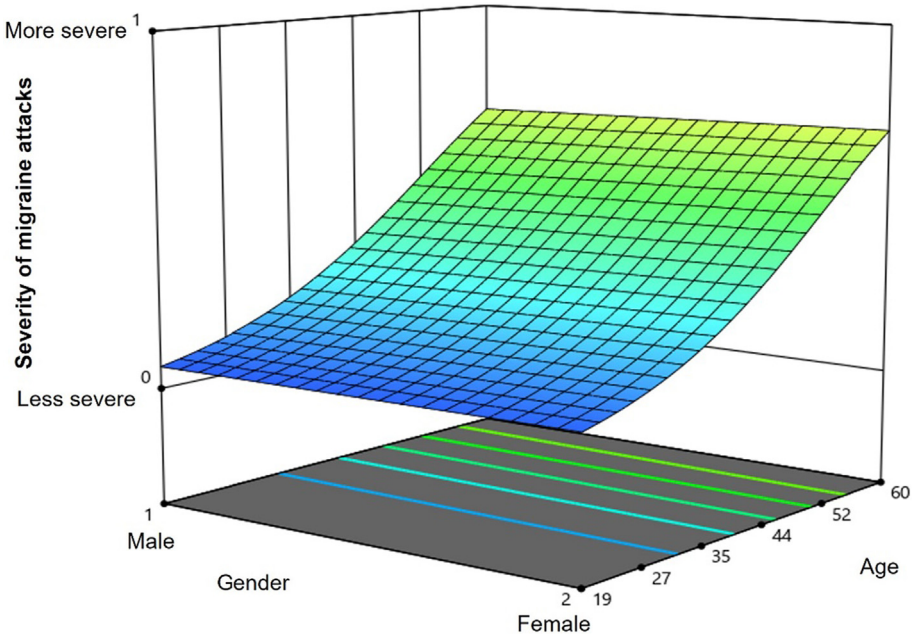

Fig. 2. Response surface plot showing the effect of migraine history and subjects' age on the MIDAS score at baseline (0 months).

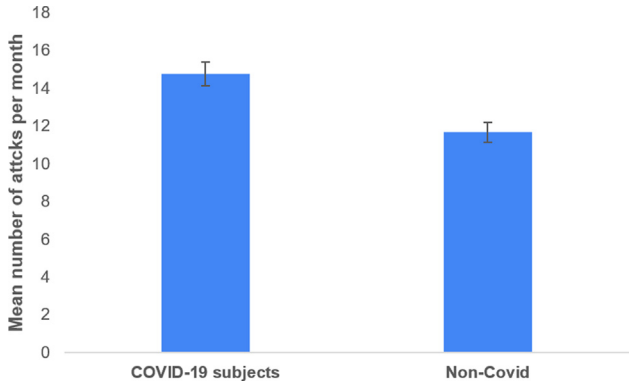

Fig. 3. Mean ± SE frequency of migraine attack per month for subjects with previous SARS-Cov2 infection compared with non-covid subjects.

previous preventative treatment failures, as well as chronic migraine patients who have had previous treatments. More recently, findings from many real-world studies have shown erenumab's efficacy and tolerability in the treatment of migraine patients who have failed to respond to earlier preventative treatments (Russo et al., 2020).

The current study found no significant difference regarding the MIDAS value among subjects who received prophylactic therapy compared with those who did not receive any therapy before Erenumab. In this line, a previous study (Goadsby et al., 2019) with only data in chronic migraine patients who had failed prior preventive treatments are available, showing reductions in monthly headache days of 2.5 for monthly erenumab 70 mg administration and 3.3 for monthly erenumab 140 mg administration in patients with one prior failed medication category, and of 2.7 and 4.3 respectively for monthly erenumab 70 mg and 140 mg administration in patients with two prior failed medication categories. In contrast, Barbanti et al. (Barbanti et al., 2021) found that because it induces

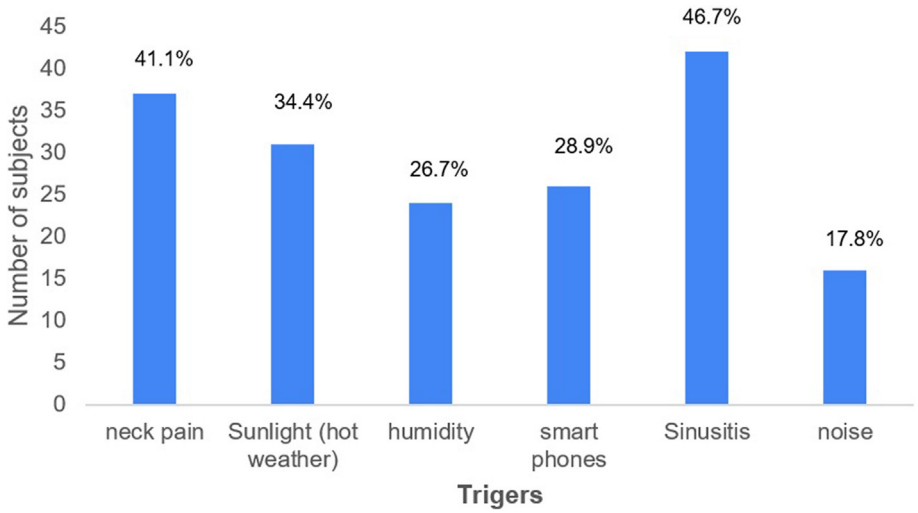

Fig. 4. Triggers that stimulate migraine attacks.

a progressive reduction in migraine frequency, use of analgesics, pain severity, and disability, and has a good safety and tolerability profile, erenumab at a dose of 70 mg was effective in patients with high-frequency episodic migraine (HFEM) or chronic migraine (CM) with three previous preventive therapeutic failures.

Higher usage of acute/preventive migraine drugs is likely to be linked to lower expectations for migraine improvement, as well as a larger illness burden. (Wang et al., 2021). This could explain why participants who got preventive therapy and those who did not get any therapy before Erenumab had similar MIDAS values.

In this study, the severity of migraine attacks was higher with the subject previously infected with SARS-CoV-2 compared to its frequency for non-covid-19 subjects. The increased severity was noted to be significantly higher with elder subjects. In agreement, Grassini et al. (Grassini et al., 2021), Arca and Starling (Arca and Starling 2020) reported a significant exacerbation of headache attacks during COVID-19 infection in a previous case report. Patients, on the other hand, developed pneumonia and reported various clinical symptoms suggestive of SARS-CoV-2-related meningoencephalitis. The exact processes underlying the rise in migraine attacks with SARS-CoV-2 infection are still unknown. Meningoencephalitis caused by a viral agent directly invading the brain, metabolic encephalopathy, and cytokine release syndrome are all possible explanations. (CRS), (Arca and Starling, 2020; Grassini et al., 2021).

The present study showed that using Erenumab resulted in a significant reduction of topiramate and shifting to traditional non-steroidal anti-inflammatory drugs (NSAIDs), percent of subjects using topiramate before starting Erenumab therapy was 87.77% that reduced to 22.2% after receiving Erenumab injections. In this regard, Tepper et al., (Tepper et al., 2021) found Erenumab treatment was linked to a significant reduction in the number of monthly acute headache medication days (HMD) in the key episodic migraine (EM) and chronic migraine (CM) studies (CM). At baseline, non-migraine-specific medication days (non-MSMD) in non-MSM only users showed corresponding numerical reductions. The reductions in MSMD were maintained in the extension periods of the EM and CM experiments, according to further analyses. Erenumab 70 mg was linked with roughly 40% of patients obtaining a 50% decrease in monthly MSMD in both the EM and CM studies, whereas erenumab 140 mg was associated with approximately 50% of patients achieving a 50% reduction in monthly MSMD in both investigations. In both EM and CM, erenumab was linked with a larger number of patients attaining a 50%, 75%, and 100% reduction in monthly MSMD, however achieving a 100% response is a very difficult aim, especially in patients with CM.

Regarding the safety concerns of Erenumab therapy, our subjects reported that skin redness and local pain were the most common adverse effects 63.3%, 47.77% respectively, while 31.1% reported constipation to be the adverse effect. While nasopharyngitis and upper respiratory infection represent (15.5%) and (11.1%) respectively but none of these adverse events lead to therapy discontinuation. The most common triggers that were reported to stimulate migraine attacks were sinusitis, neck pain, sunlight (hot weather). In agreement with the STRIVE, ARISE and Tepper et al. trials (Mitsikostas and Reuter, 2017), reported that 25 participants experienced severe adverse events as a result of erenumab injection, with nasopharyngitis, upper respiratory tract infection, sinusitis, and injection site discomfort being the most common. Nasopharyngitis, upper respiratory tract infection, injection-site pain, nausea, influenza, migraine, constipation, exhaustion, sinusitis, arthralgia, urinary tract infection, back pain, and muscle spasms were among the adverse events reported in the three clinical studies. Other findings by Buse et al. (Buse et al., 2010) noted that Migraine has been linked to depression and anxiety in numerous studies. Although the existence of common pathophysiological mechanisms is still debated, it is well understood that depressive and anxious conditions make migraine treatment more difficult and are linked to negative outcomes such as increased rates of chronic migraine onset or progression, decreased quality of life, and increased overall disease burden. (Ashina et al., 2012). As with previous studies of erenumab in migraine prevention, the rate of adverse events reported in these studies (Goadsby et al., 2017; Sakai et al., 2019) for erenumab was generally low and similar to placebo, and the trial was halted owing to adverse occurrences was low. Study population features, ethnic and regional disparities, and study design changes may represent a larger expectation of disease management improvement with an agent that has been shown to be effective in prior studies.

4.1. Limitation of this study

The trial's maximum duration was six months and there was no placebo group which could be a drawback. In long-term outcome research, the safety and effectiveness characteristics of erenumab may vary. Another weakness of this study was that they only looked at one erenumab dose when looking at dose dependency. If the clinical studies had been conducted with more dosages, the efficacy and safety outcomes might have been different.

5. Conclusion

Using Erenumab therapy showed a great beneficial impact regarding the reduction of migraine-related disabilities. Sinusitis and neck pain are the main triggers for stimulation of migraine for participating subjects. Besides, previous infection with SARS-CoV-2 was related to the increased severity of migraine attacks during the infection represented as increased frequency of migraine attacks. Regarding the safety of Erenumab therapy, there were no serious manifestations related to the therapy and it was highly tolerable compared with the traditional therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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