Received: 19 August 2022 | Revised: 10 January 2023 | Accepted: 10 January 2023

DOI: 10.1111/epi.17508

Epilepsia®

RESEARCH ARTICLE

Levetiracetam as a first-line antiseizure medication in WHO grade 2 glioma: Time to seizure freedom and rates of treatment failure

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Funding information
Leeds Teaching Hospitals; Yorkshire's Brain Tumor Charity

Abstract

Objective: The high seizure burden seen in World Health Association (WHO) grade 2 gliomas is well documented. This study aims to identify factors that influence the probability of seizure freedom (12 months of seizure remission) and treatment failure (antiseizure medication [ASM] cessation or introduction of an alternative) in patients with WHO grade 2 glioma.

Methods: This is a retrospective observational analysis of patients from a regional UK neurosurgical center with histologically proven ($n = 146$) WHO grade 2 glioma and brain tumor related epilepsy. Statistical analyses using both Kaplan-Meier and Cox proportional hazards models were undertaken, with a particular focus on treatment outcomes when the commonly prescribed ASM levetiracetam ($n = 101$) is used as first line.

Results: Treatment with levetiracetam as a first-line ASM resulted in a significant increase in the probability of seizure freedom ($p < .05$) at 2 years compared with treatment with an alternative ASM. Individuals presenting with focal seizures without bilateral tonic-clonic progression were between 39% and 42% significantly less likely to reach seizure freedom within 10 years ($p < .05$) and 132% more likely to fail treatment by 5 years ($p < .01$) when compared to individuals who had seizures with progression to bilateral tonic-clonic activity. ASM choice did not significantly affect treatment failure rates.

Significance: More than two-thirds of patients with WHO grade 2 glioma related epilepsy treated with levetiracetam first line achieve seizure freedom within 2 years and it is a reasonable first-choice agent. Experiencing mainly focal seizures without progression infers a significant long-term reduction in the chance of seizure freedom. Further studies are needed to inform ASM selection.

KEYWORDS

epilepsy, glioma, levetiracetam, neuro-oncology, seizures

1 | INTRODUCTION

Gliomas are a heterogenous group of primary brain tumors arising from glial cell types. According to Cancer Research UK, more than 12 000 people are diagnosed with a primary brain tumor each year in the UK.[1] Primary brain tumors are further defined by the World Health Organization (WHO) Glioma Classification, with grades 1 and 2 categorized as "low grade" and grades 3 and 4 as "high grade."[2] WHO grade 2 gliomas are considered low grade in nature but are thought to inevitably progress to high grade with time. Until the updated WHO classification of 2016, tumors were identified primarily by histological appearance. More recently, the rise of tumor genotyping has become the dominant factor in determining how tumors are classified. Two major histological subtypes of WHO grade 2 tumors are diffuse astrocytoma and oligodendroglioma.

Epilepsy is a common manifestation in WHO grade 2 glioma. Despite their usually slower trajectory of growth there is a strikingly high incidence of tumor-associated seizures in this patient population. Estimations of epilepsy prevalence in WHO grade 2 glioma vary, although in the 60%–90% of patients are thought to have tumor-related seizures.[3,4] In contrast, only 30%–60% of patients with high-grade tumors such as glioblastoma multiforme have a diagnosis of epilepsy.[5] This stark contrast in rates of seizures suggests that either different or additional mechanisms of seizure generation exist in low-grade tumors compared with their high-grade counterparts. Tumor invasion and destruction of cortical networks via deafferentation or compromise of vascular supply alone are unlikely to be the sole processes by which seizures are generated or provoked.[6] Glioma-specific mechanisms of epileptogenesis have been proposed involving the excitatory transmitter glutamate. These range from impairment in transport and clearance of glutamate to molecular mimicry of its action following mutations in the isocitrate-dehydrogenase 1 gene (IDH1) leading to production of aberrant compounds such as 2-hydroxyglutarate (2-HG).[7,8]

Because this patient group experiences a high seizure burden and considering the high likelihood of novel and tumor-specific pathophysiology driving this, attention has turned to how best treat symptomatic seizures in low-grade tumor-related epilepsy. At present, there is no universally accepted protocol in terms of which antiseizure medication (ASM) may be most appropriate in terms of efficacy and tolerability in seizures of this nature. Levetiracetam, lamotrigine, and topiramate have all been suggested as potentially appropriate first-line ASMs in tumor-related epilepsy.[9–11] Due to the high frequency of concurrent prescribing of both chemotherapeutics and other drugs such as corticosteroids, certain ASMs are less utilized due to drug–drug interactions, although they are still prescribed in tumor-related epilepsy in select patients. ASMs such as carbamazepine and phenytoin may be effective but are likely to interfere with other treatments, predominantly due to their interactions with hepatic enzymes. Sodium valproate has fewer drug interactions and has been used effectively in tumor-related epilepsy, although it may increase the risk of chemotherapy-induced thrombocytopenia, leukopenia, and neutropenia when taken in combination with temozolomide chemotherapy.[12] Other, less commonly used ASMs, have been trialed in small retrospective and prospective studies including lacosamide, pregabalin, and perampanel.[13–15]

In most trials of the ASMs mentioned, patient selection with regard to brain tumors is relatively broad. Many group together both low- and high-grade gliomas as "brain tumor–related epilepsy" within the treatment arms. Given that high-grade glioma is more common than grade 2 glioma, and the probable differences in tumor physiology described previously, there is a relative lack of information on ASM efficacy, specifically in patients with WHO grade 2 glioma.

Key Points

What is already known on this topic

- There currently exists little consensus with regard to the optimal first-line antiseizure medication in epilepsy secondary to World Health Organization (WHO) grade 2 glioma.

What this study adds

- The use of levetiracetam as first-line treatment results in roughly one-third of patients reaching seizure freedom at 12 months, with more than two-thirds having achieved seizure freedom at 24 months.
- Patients with focal to bilateral tonic-clonic seizures have a significantly increased chance of reaching seizure freedom in the long term.

How this study might affect research, practice or policy

- Levetiracetam is an appropriate first-line agent in this specific patient population.
- Seizure type should be considered as a strong indicator of the probability of future seizure freedom.

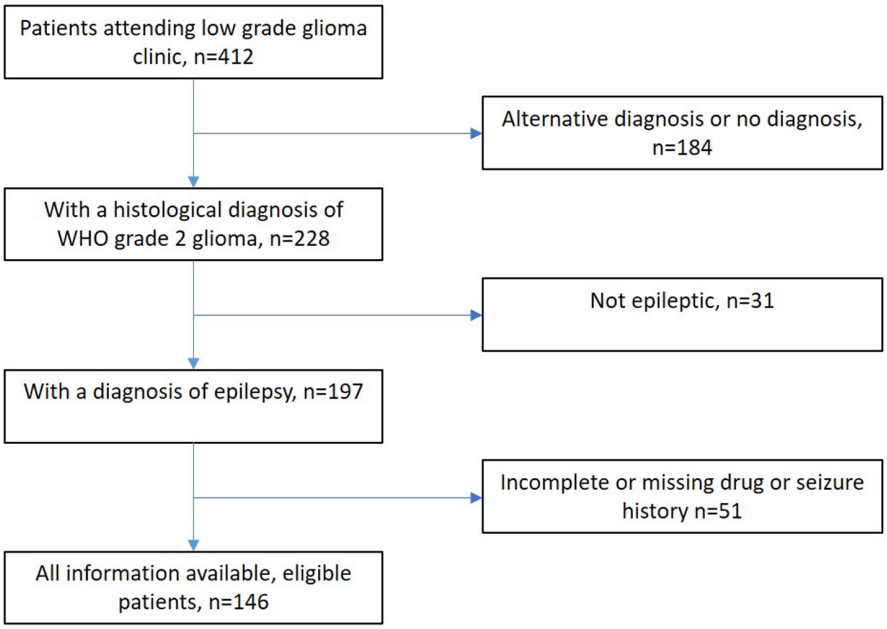

FIGURE 1 Flow diagram of patient selection criteria

Levetiracetam is one of the most commonly prescribed ASMs. It is thought to exert its action by targeting the synaptic vesicle protein 2A (SV2A), although the precise function of this protein and how levetiracetam is able to utilize it remain unclear.[16] Due to its efficacy against a range of seizure types it is a first-line agent in generalized epilepsy syndromes in the broader epilepsy population. It is generally well tolerated in terms of drug-induced side effects and is relatively simple to commence and titrate. It is also included in many protocols for status epilepticus. In focal epilepsy, levetiracetam has also long been considered effective, although a recent randomized-controlled trial (SANAD II study) comparing levetiracetam, lamotrigine, and zonisamide in newly diagnosed focal epilepsy ultimately found lamotrigine to be the most optimal ASM.[17] In addition, the other arm of the SANAD II study compared levetiracetam with sodium valproate in generalized or unclassified newly diagnosed epilepsy.[18] It found that levetiracetam did not meet the criteria for noninferiority compared with sodium valproate.

In patients who experience seizures secondary to a low-grade glioma, focal seizures without progression to bilateral tonic-clonic activity (FwP seizures) are most common.[19] it is unclear if FwP seizures secondary to a tumor respond to ASM treatment as other focal epilepsy syndromes do. The term "generalized onset" implies a seizure that according to the International League Against Epilepsy (ILAE) classification "rapidly engages bilaterally distributed networks."[20] Seizures may also be classified as "focal to bilateral tonic-clonic" (FBT-C seizure), previously termed seizure with secondary generalization, where the initial manifestation of the seizure is focal (e.g., *déjà vu* or unilateral motor activity) with subsequent progression to generalized tonic-clonic activity. For our study, we have distinguished between patients who have FwP seizures and those who progress to an FBT-C seizure, with the assumption that all seizures have a focal onset at least initially.

We aimed to examine how levetiracetam performed with regard to treatment outcomes (probability of inducing seizure freedom, the time to seizure freedom and rates of treatment failure) in a population with histologically proven WHO grade 2 glioma. Moreover, we examined the relationship between the seizure semiology and treatment outcomes as well as histological, surgical, and patient demographic factors.

2 | MATERIALS AND METHODS

2.1 | Patient selection

We undertook a retrospective analysis of patients presenting to a low-grade glioma clinic at a National Health Service (NHS) regional neurosurgical center. Inclusion criteria for the study were as follows: (1) age ≥16 at the time of diagnosis, (2) histologically proven either diffuse astrocytoma or oligodendroglioma, (3) a diagnosis of epilepsy presumed to be related to the glioma, and (4) use of an ASM with the intention to treat brain tumor–related seizures. Of 412 patients recorded as attending the low-grade clinic, 146 fit the study criteria. A flow diagram of the patient selection process can be seen in Figure 1.

2.2 | Data collection and study design

This is a retrospective observational study. The electronic medical records of each patient were searched to establish basic patient demographics, a timeline of the disease course (age at diagnosis, survival time, time of surgery, and follow-up period), histology/genetic results (tissue/genetic diagnosis), epilepsy information (date of epilepsy diagnosis and predominant seizure type), and ASM use (first ASM prescribed, treatment failure time, reason for treatment failure, and number of ASMs tried in total). The date distribution of records searched was January 1997 to December 2021. Preliminary data included coarse lobe-based location tags for each tumor; however, early analysis showed that all regions except brainstem or cerebellar tumors were more likely to be associated with seizures. In addition, the size of these tumors often caused several locations to be involved thereby making categorization difficult. Tumor volume was not assessed.

Patient age at diagnosis ranged from 18 to 71 years. Seizure type was coded as "FwP," "FBT-C," or "unknown," based on descriptions from clinic letters, ambulance records, and hospital notes, with the most predominant type (not the first) experienced by the patient being used.

2.3 | Statistical analysis software

The study data were anonymized at collection. They were then coded to allow analysis in the statistical software package 'R' (available via https://www.r-project.org/, version 4.1.2).

2.4 | Model and variable selection

Kaplan-Meier analysis was performed in *R* to provide a visual depiction of rates of (1) seizure freedom and (2) treatment failure between levetiracetam and alternative ASM groups. Seizure freedom was defined as 12 months without seizures. Patients were censored if they were lost to follow-up. An intention-to-treat approach was taken, meaning patients remained in their original cohort regardless of treatment failure. Treatment failure of a first ASM was defined as either cessation of the ASM for any reason or addition of another ASM for reasons of seizure control (polytherapy). A Kaplan-Meier model with censoring at treatment failure was considered; however, in order for Kaplan-Meier analysis to be valid, an assumption is made that censoring is noninformative—that it occurs not because of any factors that could influence the outcome. Seeing as treatment failure due to uncontrolled seizures does have an obvious impact on a patient's risk of seizure freedom, this method would likely be invalid.

Further analysis was undertaken using a Cox proportional hazards (CPH) model to explore variables that may influence (1) seizure freedom and (2) treatment failure. Several variables were chosen to be included in an initial CPH model for both outcomes to assess for differences between the levetiracetam and alternative ASM cohorts. The additional variables included were seizure type (FwP vs FBT-C), sex, age at diagnosis, histology (diffuse astrocytoma vs oligodendroglioma), type of surgery performed (debulking vs biopsy), and time to first surgery from diagnosis. After generation of initial models, and to ensure appropriate variable selection, analysis of variance (ANOVA) was carried out using the "likelihood ratio test" (LRT) to see whether inclusion of specific variables led to any improvement in the model. Using this method it was found that the *type of surgery performed*, *sex*, *histology*, and *age at diagnosis* variables all failed to make any significant contribution to either model, and so these were excluded from further modeling. That surgery type did not influence outcome is likely because a vast majority of patients had debulking surgery. The *time to first surgery* variable made no significant contribution to the treatment failure model and was also excluded from this section.

An assumption of the CPH model is that the hazards remain constant over time. We checked this in our models by calculating Schoenfeld residuals in *R*. The *time to first surgery* variable appeared to violate the presumptions of proportional hazards but improved the model estimates when included in the time to seizure-freedom model. To overcome this, the *time to first surgery* variable was stratified so that it could be included in the final model. All remaining variables in the models produced Schoenfeld residuals with non-significant *p*-values, allowing the use of a proportional hazards approach.

2.5 | Ethical considerations

No new data were being generated by this study and this was a retrospective review of medical case notes. The study methods were reviewed by the local Information Governance and Caldicott teams with a Caldicott letter of approval being issued sanctioning the study. All patient-sensitive data were stored password protected via secure NHS servers and according to local policy.

3 | RESULTS

3.1 | Patient demographics and seizure type

The average age at diagnosis at our center was 39.9 years. The majority of patients were male (102 male, 44 female). Average follow-up time was 6.29 years, with the median year of diagnosis being 2015 (only nine patients were diagnosed pre-2005). The median time from first seizure to ASM initiation was 38 days and from radiological diagnosis to ASM initiation was 11 days, likely reflecting the average time to neuroimaging. Predominantly FwP seizures were experienced by 79 patients (54.1%), whereas 67 had mostly FBT-C (45.9%). Histological evaluation showed that 71 patients (48.6%) had an oligodendroglioma and 75 (51.4%) had diffuse astrocytoma. Chemotherapy was received by a similar number of levetiracetam group patients (35/101, 34.7%) and alternative ASM group patients (17/45, 37.8%) at some point during follow-up. Carbamazepine or phenytoin was given to five patients who also received chemotherapy. All five had either reached seizure freedom or failed treatment by the time of chemotherapy, negating this potential interaction. The median time from ASM initiation to administration of chemotherapy in those that received it was 1037 days.

3.2 | Kaplan-Meier analysis of 2-, 3- and 5-year seizure freedom

Of 146 patients with confirmed, diffuse astrocytoma or oligodendroglioma, 101 were prescribed levetiracetam as first line treatment, with the remaining 45 patients prescribed an alternative ASM. The "alternative ASM" group was prescribed various commonly available ASMs (carbamazepine $n = 16$, lamotrigine $n = 15$, sodium valproate $n = 9$, topiramate $n = 3$, and phenytoin $n = 2$).

Kaplan-Meier analysis was performed to compare seizure-freedom times between the levetiracetam as a first ASM group and the alternative first ASM group (Figure 2).

Chi-square testing was performed to assess for significance between the two groups at 2-, 3-, and 5-year intervals. A significant difference was detected at 2 years ($p = .005$, 1 df) and 3 years ($p = .01$, 1 df), with levetiracetam increasing the probability of seizure freedom. No significant difference was seen at 5 years ($p = .08$, 1 df).

3.3 | Kaplan–Meier analysis of treatment failure

In total, 33 of the 101 levetiracetam patients failed treatment within 5 years of ASM commencement (with

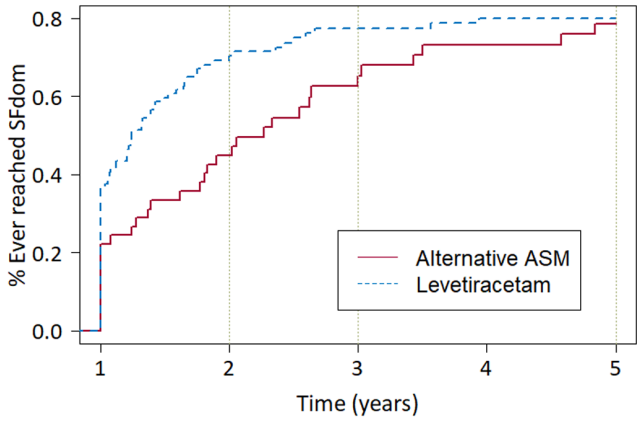

FIGURE 2 Kaplan-Meier analysis of seizure freedom when given levetiracetam vs an alternative first-line ASM in grade 2 glioma. Dotted lines (green) at 2-, 3-, and 5-year intervals from first ASM administration. ASM, antiseizure medication; SFdom, seizure freedom

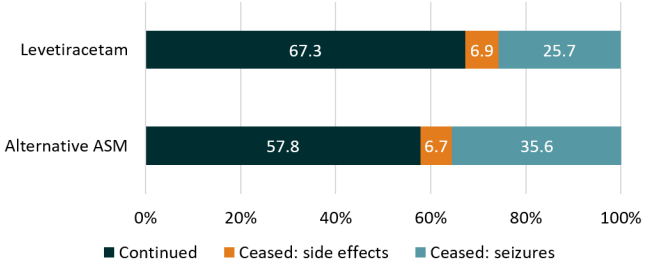

FIGURE 3 Reasons for treatment failure over 5 years in levetiracetam groups vs alternative ASM group. ASM, antiseizure medication

treatment failure defined as cessation of the first ASM or addition of a second agent). Of patients who failed treatment, 7 (21.2%) had side effects or an adverse event listed as the cause, with 26 (78.8%) failing due to poor seizure control. In the alternative ASM group, 19 participants failed treatment within 5 years. Of these, 3 (15.8%) were due to side effects or adverse events and 16 (84.2%) to poor seizure control. In both groups, roughly four in five patients who failed treatment did so for reasons of seizure control (Figure 3). Treatment failure rates between the two groups were plotted in a Kaplan-Meier analysis (Figure 4).

Figure 4 shows that at all time points over 5 years a similar proportion of patients in each group failed treatment (e.g., roughly 15% at 1 year and 25% at 2 years). Chi-square testing here gives $p = .5$ (1 df) suggesting that no significant difference in the rate of treatment failure exists between the two groups.

The similar treatment failure rates (and similar reasons for failure), coupled with the lack of a statistically

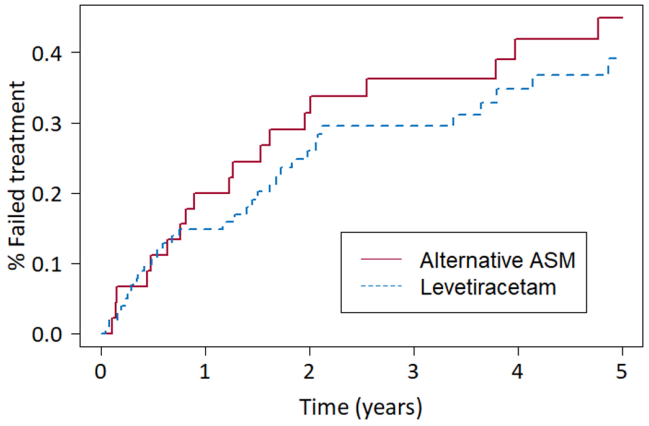

FIGURE 4 Kaplan-Meier analysis of ASM treatment failure in grade 2 glioma. ASM, antiseizure medication

TABLE 1 Influence of levetiracetam as a first-line ASM and seizure type on the probability of seizure freedom at 2, 3, 5, and 10 years from commencement of ASM

	p-value	Hazard ratio and 95% CI
Levetiracetam as first-line ASM		
SFdom 2 years post ASM start	.02*	1.76 [1.06–2.94]
SFdom 3 years post ASM	.06	1.57 [.99–2.50]
SFdom 5 years post ASM	.21	1.32 [.86–2.03]
SFdom 10 years post ASM	.16	1.36 [.88–2.09]
FwP seizure type		
SFdom 2 years post ASM	.02*	.61 [.40–.94]
SFdom 3 years post ASM	.009**	.59 [.39–.88]
SFdom 5 years post ASM	.006**	.58 [.39–.86]
SFdom 10 years post ASM	.006**	.58 [.39–.85]

Abbreviations: ASM, antiseizure medication; CI, confidence interval; FwP, focal seizures without progression to bilateral tonic-clonic activity; SFdom, seizure freedom.

*$p \leq .05$; **$p \leq .01$.

significant difference between the groups, strengthens the notion that the difference demonstrated in Figure 2 is not being distorted by excessive rates of treatment failure or ASM intolerance in one treatment group more than the other.

3.4 | Cox proportional hazards model of seizure freedom

Using a Cox proportional hazards model, the influence of included variables on the time taken to reach seizure freedom over a 2-, 3-, 5-, and 10-year period was assessed. These results are outlined in Table 1.

At the 2-year time interval, levetiracetam as a first ASM was associated with a significant increase in the probability of seizure freedom ($p = .02$), with 69 of 96 patients followed up (5 censored) reaching seizure freedom. This compares with 20 of 44 patients (1 censored) becoming seizure-free in the alternative ASM group. Being given levetiracetam meant patients were 76% more likely to be seizure-free at 2 years than with an alternative ASM. This effect was not significant at the 3-, 5-, and 10-year intervals. Predominant seizure type was highly significant when predicting seizure freedom at all time intervals. At 2 years following first ASM administration, those with predominantly FwP seizures were 39% less likely than those with FBT-C seizures to have reached seizure freedom. The improved seizure prognosis seen with FBT-C seizures appeared to be fairly constant across all 10 years of follow up.

3.5 | Cox proportional hazards model of treatment failure

A CPH model comparing the risk of treatment failure over a 5-year period was produced. Seizure type was shown to have a significant effect on the likelihood of treatment failure, with patients experiencing predominantly FwP seizures much more likely to fail treatment than those reporting FBT-C seizures ($p = .006$, hazard ratio [HR] = 2.32, confidence interval [CI] 1.27–4.26). This translates to patients with FwP seizures being 132% more likely to fail treatment within 5 years. Use of levetiracetam as a first-line ASM did not demonstrate a significant change from the risk of treatment failure when compared to alternative ASMs ($p = .82$, HR = .94, CI .53–1.66).

3.6 | Number of ASMs prescribed

For each patient the total number of different ASMs prescribed was recorded. However, these values needed to be adjusted as they are amassed over a total follow-up period that can be 10 years or more for some patients (unlike the previous analyses calculated over the first 5 years for both groups). When an ASMs/year of follow-up average was calculated, the levetiracetam group was prescribed roughly .31 ASMs/year of follow-up, with .24 ASMs/year for the alternative ASM group. This suggests that polytherapy may eventually be more common in the levetiracetam group than in the alternative ASM group.

4 | DISCUSSION

Levetiracetam is the most widely prescribed first-line ASM in patients with grade 2 glioma at our institution, and this is likely mirrored elsewhere.[21] There is a need for further

evidence as to which of the commonly prescribed ASMs is most effective in this patient group and whether applying similar treatment strategies informing ASM choice in other forms of epilepsy is reasonable.

We found a significant treatment effect for levetiracetam at 2- and 3-year intervals in the Kaplan-Meier analysis and at only 2 years with the CPH approach. In the Kaplan-Meier analysis of seizure-freedom rates between the two groups we have opted to use an intention-to-treat approach, meaning that patients stay in their original cohort despite treatment failure at any stage. If patients are not seizure-free after a few years on any ASM it is likely an additional or alternative agent will have been prescribed. This makes it likely that the majority of the patients with ongoing seizures beyond 2–3 years in Figure 2 will have been switched to an alternative or additional ASM. This may explain the narrowing seen in the difference between the two cohorts, starting at roughly 2.5 years, as patients with ongoing seizures in the "alternative ASM" group are likely to have been switched to a different first-line ASM (which may be levetiracetam). It may be that the alternative ASM group contains one or more ASMs that are much less effective in this patient group. For this reason, the better performance of levetiracetam overall should not be taken as showing its superiority over all ASMs in the alternative group. Instead, this study adds important information with regard to the likely efficacy of levetiracetam on seizure outcomes at various time points when given first line to this specific patient population. Our study suggests that roughly two-thirds of patients treated with levetiracetam first line could expect to be seizure-free at 2 years. It is also worth considering that despite meeting the criteria for "treatment failure" in our study, an ASM may be continued alongside a new introduction and still contribute in part to reduction of overall seizure risk. For this reason, there is a possibility that polytherapy may play a part in the results seen in Figure 2. Despite treatment failure rates being similar between the two groups, analysis of the average "ASMs/year of follow-up" data suggests that levetiracetam may be more likely to be continued alongside a newly introduced agent than one of the alternative ASMs, which may be more likely to be simply swapped out. This could be a reflection of local practices at our institution.

The CPH model of seizure freedom also demonstrated a higher rate of seizure freedom in the levetiracetam group at the 2-year mark. When creating the models, we found that time to seizure freedom was influenced by how soon after diagnosis the patient had surgery. This makes sense given the well-documented antiseizure effect of surgery in grade 2 glioma, which appears to increase with extent of resection.[22] The Kaplan-Meier model does not control for any additional variables, unlike the CPH method. For this reason, the CPH model is likely more reflective of reality, as it was able to take into account both the time to surgery and seizure type.

Focal seizures can often be more difficult to treat when compared with generalized seizures in many forms of epilepsy. It is, therefore, interesting to see that our study demonstrates via the CPH model that seizure type appears to give a fixed effect over time influencing the likelihood of both seizure freedom and treatment failure. At each time interval a patient was between 39% and 42% less likely to attain seizure freedom if they had predominantly focal seizures without bilateral tonic-clonic spread. It is worth noting that when collecting the data, we found that most patients in this population had very stereotyped seizure semiology with very few exhibiting a mixed picture, which was difficult to categorize. The fact that this difference between seizure types persists for up to a decade suggests that not only is ASM therapy much less effective against FwP seizures but that debulking surgery may also have more antiseizure effect against seizures that generalize to involve bilateral tonic-clonic activity vs those that do not. As a debulking procedure is likely to cause widespread disruption to cortical networks in the vicinity of the tumor, it is possible to see how bilateral tonic-clonic seizures may be more readily averted via a postoperative reduction in connectivity—even though not all tumor tissue can be resected due to their infiltrating nature. Whether patients convert from seizures with bilateral tonic-clonic activity to FwP seizures post-surgery is not deducible from the data collected here.

Levetiracetam is seen widely as a generally well-tolerated ASM. In our analysis we found that roughly one in five patients were unable to tolerate it due to either side effects or an adverse event. There was no difference ($p = .63$) between the two groups in terms of reasons for failing treatment, and therefore, levetiracetam did not stand out as an ASM with superior tolerability as might commonly be assumed. We did not collect dose information for the various ASMs. There will certainly be a range of doses on which a variety of patients (weights, renal function, hepatic function, competing drugs) will be maintained. We have no reason to suspect our institution has any atypical policies regarding ASM dosing. Furthermore, this patient cohort is, in our experience, often proactively managed by epilepsy specialist nurses and so instances of underdosing are likely to be uncommon.

Preliminary data included location tags for each tumor. Early analysis suggested that all glioma locations, except for those in the brainstem or cerebellum, were likely to be associated with the development of seizures (including

occipital lobe tumors). Tumor location was, therefore, not included as a variable in our final analysis.

5 | CONCLUSION

Our study suggests that levetiracetam is a suitable first-line ASM in the treatment of seizures in grade 2 glioma. More than 60% of patients prescribed levetiracetam achieved seizure freedom within 2 years. Levetiracetam was more efficacious at 2 years when compared with a group of alternative first-line ASMs, though further comparative prospective studies are needed to ascertain which drug is the most efficacious initial treatment. A history of predominantly FBT-C seizures in patients with grade 2 glioma is a significant predictor of seizure freedom, which seemingly persists for up to a decade and despite surgery.

AUTHOR CONTRIBUTIONS

The study was designed by SF, RM, and MM. SF, JG, PC, and RM collected the data. Data analysis was performed by SF and interpreted by SF, RM, and MM. All authors were involved in drafting the manuscript and have read and approved the final version.

ACKNOWLEDGMENTS

SF wishes to acknowledge RM and MM for supervising and supporting his medical doctorate.

FUNDING INFORMATION

SF is a post-doctoral researcher funded by Leeds Teaching Hospitals NHS Trust. RM receives research funding from Yorkshire's Brain Tumor Charity and Candlelighters.

CONFLICT OF INTEREST

SF has delivered a paid lecture of his own work for UCB Pharma. All other authors have no declarations to make in relation to this work.

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How to cite this article: Fairclough S, Goodden J, Chumas P, Mathew R, Maguire M. Levetiracetam as a first-line antiseizure medication in WHO grade 2 glioma: Time to seizure freedom and rates of treatment failure. Epilepsia. 2023;00:1–9. https://doi.org/10.1111/epi.17508