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Pharmacotherapy of Rasmussen's Encephalitis: A Comparison of Epilepsia Partialis Continua with Rituximab and Azathioprine

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Abstract

Rasmussen's Encephalitis is a rare neurological condition causing inflammation of the brain, which thereafter can result in seizures, neuronal death, and significant neurological deficits. Its exact cause is unknown and it typically presents in children. The best known treatment is a surgical hemispherectomy to prevent the spread of inflammation, however this is invasive and not without risk. The best therapeutic approach has been with immunomodulation using the antimetabolite agent, azathioprine. Monoclonal antibodies such as rituximab have shown promise in early clinical trials for the treatment of Rasmussen's Encephalitis, but little has been done to compare the efficacy of rituximab versus azathioprine.

A systematic review was then conducted with a study in which patients were treated with rituximab for Rasmussen's Encephalitis (RE) compared to a study in which patients were treated with azathioprine. The presence of focal encephalitis characterized by epilepsia partialis continua (EPC) was measured in both studies following the treatments.

Azathioprine and Rituximab both had statistically significant effects on decreasing the incidence of epilepsia partialis continua when compared to their respective controls. However, rituximab seemed to have a greater effect on reducing the incidence of EPC than azathioprine.

Rituximab seems to have an immense potential in reducing EPC in patients with RE. For this review, Rituximab seemed to have a greater reduction in EPC than azathioprine. Further studies with greater sample sizes assessing reductions in the several other complications of RE must be conducted in order to confirm whether or not Rituximab is truly a better choice than Azathioprine.

Keywords: Encephalitis; Rasmussen's; Rituximab; Azathioprine; Monoclonal Antibodies

1. Introduction

Rasmussen's encephalitis is a rare chronic neurological disorder, characterized by unilateral inflammation of the cerebral cortex, drug-resistant epilepsy, and progressive neurological and cognitive deterioration (1). Neuropathological and immunological studies support the notion that Previous studies support the notion that Rasmussen's encephalitis is probably driven by a T-cell response to one or more antigenic epitopes, with potential additional contribution by autoantibodies (1).

Immunomodulatory treatments have traditionally been the mainstay of treatment and have previously shown promise with at least slowing the progression of the disease (1). The main clinical feature that is assessed in studies is the intractable focal seizures, also known as Epilepsia Partialis Continua (EPC) (2). Azathioprine, an inhibitor of purine synthesis, inevitably reducing clonal proliferation of lymphocytes has been previously shown to be effective in the

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reduction of EPC (2). More recently , rituximab, an anti-CD20 monoclonal antibody targeting B cells to inhibit their proliferation and reduce antibody production, has also shown efficacy in controlling symptoms and disease progression (2).

While both Azathioprine and Rituximab seem to be prudent treatments in reducing EPC in patients with Rasmussen's Encephalitis, very little has been done to compare the two. It is quintessential to pinpoint the best pharmacotherapy to treat this illness, as no cure has yet been discovered.

2. Methods

For the Study with Rituximab:

Patients with continuous EPC, frequent seizures, and recurrent episodes of status epilepticus, and those with minimal or no motor deficit, or RE involving the dominant hemisphere and those who were ineligible for resective surgery received rituximab (3). A total of 17 patients ended up meeting this criteria (3). Rituximab infusion was prepared with 0.9% sodium chloride to make a final concentration of 2 mg/ml (3). Infusions were delivered at a rate of 25 mg/hour and were able to be increased by increments of 25 mg/hour every 30 mins to a maximum of 200 mg/hour as tolerated (3). The dose of rituximab used was 375 mg/m2 body surface area weekly for 4 weeks at induction followed by a single dose every six months (3). The endpoints of the study were to find the usefulness of rituximab in controlling seizures, control of EPC, prevention of progression or reversal of motor deficits, as well as the impact on MRI lesions (3).

For the Study with Azathioprine (AZA):

For this analysis, RS patients were divided into two groups – an AZA treated group and a non-treated (control) group (4). For the AZA group a minimum time of treatment of 3 months was chosen based on the drug's mechanism of action, which requires this time to reach efficacy. The decision to use AZA was made when there was a certain diagnosis of Rasmussen syndrome (4). In the initial phase, this was initiated subsequent to a trial of steroids; in the majority of patients, it was initiated when the diagnosis was confirmed and steroids initiated (4). The patients in the AZA group received open-label AZA (1.5mg/kg/day orally) for six weeks (4).

3. Results:

For the Study with Rituximab:

Figure 1: Magnetic Resonance Imaging Following Treatment

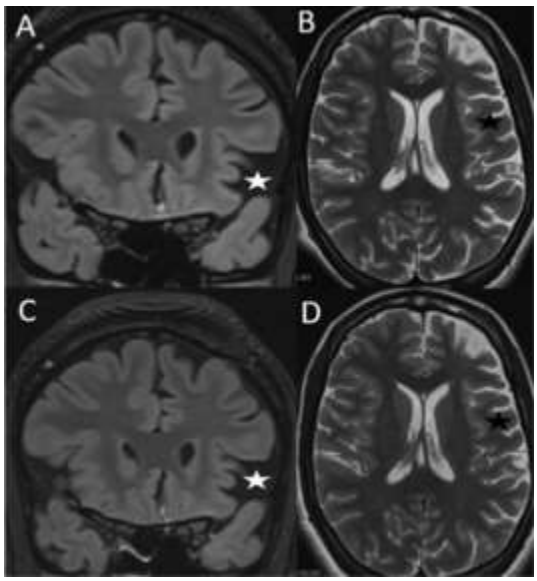

Figure 1 A) FLAIR Coronal & B) Axial T2 W image showing left frontal and perisylvian cortex atrophy (star) C) FLAIR Coronal & D) Axial T2 W image showing no progression of left frontal and perisylvian cortex atrophy (star) at 13 month follow up (case 8) (1)

All patients without any deficits at time of onset, did not develop further deficits (1). EPC resolved in four patients, but continued in two patients (1). In one patient, motor deficits improved completely while in another patient, the deficit remained static (1). A post-rituximab MRI was performed after 12 months in five patients, which showed minimal or no progression of hemispheric atrophy compared to previous MRIs (1). When rituximab was compared early in the course (within 12 months of onset of EPC, 5 patients) versus late (4 patients), two patients in the early group were found to be seizure-free compared to one in the late group (1).

For the Study with Azathioprine (AZA):

AZA was well tolerated; only 1 patient discontinued treatment due to pancytopenia (2). Patients receiving AZA had a lower prevalence of EPC (42% vs 67% in controls) and hemiparesis (64% vs 92%, respectively) (2). Cox regression showed for the AZA group compared to controls a delayed time to (1) EPC (≈2 years, exp[B] = 0.295, 95% confidence interval [CI] 0.108–0.807; p = 0.017), (2) hemiparesis (≈1 year, exp[B] = 0.315, 95% CI 0.137–0.724; p = 0.007), and (3) surgery (≈2 years, exp[B] = 2.068, 95% CI 1.012–4.227; p = 0.046) (2). However, there were no group differences in cognitive decline over time (IQ change per year) or in hemispheric gray matter atrophy on serial MRI scans (2).

4. Conclusion

Both studies suggest that azathioprine and rituximab have significant effects on reducing EPC in patients with Rasmussen's Encephalitis. Azathioprine, however, seemed to only reduce or slow the progression of symptoms, while rituximab showed promise in reversing symptoms, with a patient even regaining motor deficits. With Rasmussen's Encephalitis being a rare condition, we are incredibly limited in our sample sizes for research, and more studies must be done with greater sample sizes. Longitudinal studies conducted throughout longer periods of time need to be done in order to assess if these effects are longstanding and if there are any potential side effects that might be of concern with this treatment. Since monoclonal antibody treatment is notorious for being expensive, additional efforts must be pursued in order to lower the costs. Even if there was sufficient information suggesting that rituximab was superior to azathioprine in the treatment of Rasmussen's Encephalitis, it would only be accessible to the upper class.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The studies reviewed obtained ethical approval regarding the treatment of human subjects undergoing the treatments.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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