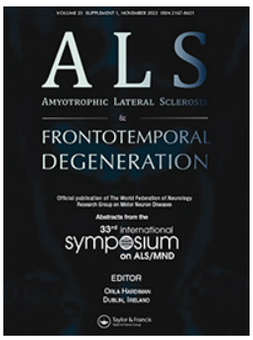

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ALSUntangled #67: rituximab

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REVIEW ARTICLE

ALSUntangled #67: rituximab

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Abstract

ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS who ask about them. Here we review rituximab, a drug which specifically depletes B lymphocytes. We show a current lack of evidence for a role of these cells in ALS progression. The one patient we found who described using Rituximab for their ALS found no benefit. Given all this, and the known serious risks of rituximab, we advise against its use as an ALS treatment.

Keywords: *ALS, rituximab, neuroinflammation, off-label treatment*

Introduction

ALSUntangled reviews alternative and off-label treatments for ALS on behalf of people living with ALS (PALS). Here we review rituximab, for which we have had 445 requests (https://www.alsuntangled.com/future-reviews/).

Background

Rituximab is a first-generation chimeric monoclonal antibody generated by fuzing a rodent Fab domain with a human Fc domain (1). It selectively targets and rapidly depletes circulating CD20+ B lymphocytes, and via this action it is used to treat

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autoimmune diseases such as rheumatoid arthritis and hematological malignancies such as chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL) (1–3). Rituximab is also increasingly utilized as a second or third line treatment for autoimmune encephalitis, neuromyelitis optica, inflammatory neuropathy and myasthenia gravis (4–7).

Mechanism

Over the past few decades, evidence has emerged to support the downstream role of neuroinflammation in the progression of ALS. Microglial activation, perivascular infiltration of monocytes and T cells, and release of proinflammatory cytokines are pathological manifestations in ALS brain and spinal cord tissues (8,9). Microglia and macrophages are the primary sources of proinflammatory molecules (10). To date, no convincing evidence has emerged supporting a direct role of B cells in ALS.

B cells are part of the adaptive immune system and lead to the production of antibodies. CD20 is a marker expressed on most B cells, including immature, naïve and mature memory B cells (11). Mature CD19+/CD20+ memory B cells express IgG on cell surface and evolve into antibody secreting plasmablasts and plasma cells. CD19+ plasmablasts are located at the periphery and have various levels of CD20 expression (12). CD38+ plasma cells reside in the bone marrow and most also express CD19+ (13). Although antibodies against gangliosides and other proteins have been detected in PALS (14,15), the function of these antibodies in ALS pathogenesis is unclear; they may simply be an epiphenomenon of neurodegeneration, rather than a cause. Indeed, B cell surface markers (CD19, CD45, CD69) and serum immunoglobulin levels do not differ between $SOD1^{G93A}$ ALS mice and wild type mice (16). Moreover, depleting B cells from $SOD1^{G93A}$ mice does not affect limb strength, onset of limb paralysis or survival time (16,17). These studies suggest that B lymphocytes play a less pivotal role in ALS progression (16,17). However, in another study using this same animal model, transfer of IL-10+ B cells decreased myeloid-derived macrophages in the central nervous system and was associated with a trend toward improved neuromuscular function (though this did not prolong survival,18). Notably, the SOD1 ALS model may not be the idea disease model because only 20% of familial and 5% of sporadic PALS carry an SOD1 gene mutation. Further studies are required to clarify whether B cells play any significant role in ALS progression.

Based on the theory that rituximab might reduce neuroinflammation (albeit with no current evidence for a specific effect of B cells in this process), we assign a TOE "Mechanisms" grade of D.

Pre-clinical models

Recent pre-clinical studies show B cells are present in the meninges and likely derived locally from calvaria (19). Moreover, pre-B cells accumulate in the spinal cord meninges of mutant SOD1 mice (20). However, we did not find published studies examining rituximab treatment in preclinical ALS models. Unpublished work suggests that intrathecal administration of rituximab IgG Fc fragment to the presymptomatic $SOD1^{G93A}$ mice lowered B cell counts and extended survival by one month (the unpublished data were obtained from Dr. Rachel Lichtenstein, contributing author of this review). Thus, we assign a TOE "Pre-clinical" grade of D.

Cases

In the online community PatientsLikeMe, we found three people who reported taking rituximab for their ALS (https://www.patientslikeme.com/treatments/detail/rituximab). The only person who provided any details stated that they perceived no benefits from this treatment (https://www.patientslikeme.com/treatment_evaluations/browse?attribute=efficacy&brand=false&condition_id=9&id=7572&value=1). Therefore, we assign a TOE "Cases" grade of F.

Trials

We found no clinical trials using rituximab in PALS. We therefore assign a TOE "Trials" grade of U.

Risks, dosing, costs

There are no data examining risks in large numbers of PALS exposed to rituximab. Significant adverse events have been documented in patients with rheumatoid arthritis, systemic vasculitis and non-Hodgkin's lymphoma treated with Rituximab, especially in the COVID era. Infusion reactions are common, which include fever, headache, pruritus, flushing, and hypotension (21). These reactions are often mild to moderate; however severe anaphylactic reactions have been reported (22). Rituximab can reactivate previous hepatitis B and hepatitis C virus infection (23,24). Therefore, testing for hepatitis B and hepatitis C infection status are recommended before drug administration. Rituximab has also been reported to cause neutropenia (25,26) and hypogammaglobulinemia (27), which further increase the associated risk of infection. Finally, rituximab can lead to progressive multifocal leukoencephalopathy (PML), a rare but severe and fatal central nervous system infection caused by JC virus (28). In light of these findings, FDA has issued black box warnings for fatal infusion reactions, severe mucocutaneous reactions, PML, and reactivation of hepatitis B infection.

Table 1. Table of evidence grades for rituximab.

	Grade	Explanation
Mechanism	D	B cells are found in CNS meninges and could theoretically influence neuroinflammation. However, depleting B cells in the mutant SOD ALS mouse model did not change disease course.
Pre-Clinical	D	We did not fund published studies of Rituximab in pre-clinical models of ALS. Unpublished data suggest intrathecal administration of Rituximab Fc fragment to ALS mouse model reduces B cell number and modestly extends survival time.
Cases	F	The only person we could find who reported on their experience with Rituximab as an ALS treatment found no benefit
Trials	U	We found no clinical trials of Rituximab in PALS
Risks	F	There is no risk data on PALS being exposed to Rituximab. More than 5% of all exposed patients in other autoimmune conditions including autoimmune neurological disorders experienced serious adverse effects.

Rituximab has been reported to have similar side effects when it is used off-label in neurological conditions (29–31). Based on the frequency of serious adverse events in various populations, we assign a TOE Grade of F (Table 1).

When it is used in rheumatoid arthritis, rituximab is administered as two 1000 mg dose IV infusions separated by 2 weeks, followed by a repeat course every 24 weeks for responders (32). In ANCA-associated vasculitis, rituximab is given as 375 mg/m^2 every week for four weeks during the induction phase (33) followed by maintenance treatment of 500 mg every six months for two years or longer (34). Both dosing strategies have been utilized in autoimmune neurological diseases. Complete B cell depletion occurs within 14 days and can last for 6–12 months. Therefore, rituximab is typically re-dosed at a 6-month interval. Recommendations vary among different diseases regarding re-dosing intervals. A fixed 6-month repeat interval and repeat course based on circulating CD19+ B cell counts have both been utilized (34,35).

The cost of rituximab treatment, including the drug and the infusion, is approximately $1000 per 100 mg (information from UpToDate).

Conclusion

Neuroinflammation is associated with disease progression in PALS. Rituximab depletes a population of immune cells, so it could theoretically help with slowing progression. However, rituximab specifically acts on B cells and the importance of these specific cells in ALS progression is still unclear; further studies are needed to elucidate this. The one person we found who reported taking it for ALS perceived no benefit. We found no trials of rituximab in ALS. Considering the side effect profile and lack of evidence to support its efficacy, we do not currently recommend the use of rituximab as an ALS treatment.

Declaration of interest

No potential conflict of interest was reported by the author(s).

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