DC Veterans Affairs Quality Improvement Project of Highly Efficacious Anti-CD 20 Disease Modifying Treatments. Side Effects-CO$T

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BACKGROUND

Introduction

- Living with, and treating multiple sclerosis (MS), is costly.
- In the US, the economic burden of MS is approximately $85.4 billion annually.[1]
- The cost of MS disease modifying treatments (DMTs), infusion centers and outpatient clinics is 80% of this burden[1].
- Highly efficacious disease modifying therapies (DMTs) have significantly reduced disability and improved MS outcomes.[2]

Purpose:

- Anti-CD20 DMTs (ocrelizumab, ofatumumab, ublituximab) and off-label rituximab, as a class, have shown to stabilize disease progression with equal effect[3,4,5,8].
- Biosimilar rituximab PVVR has more limited data, however, biosimilar rituximab PVVR suffers from its lack of clinical trial data, FDA MS disease specific approval and support or confidence for use by the MS community.
- We aimed to evaluate over a two-year period the comparative effectiveness and safety of biosimilar rituximab PVVR to FDA approved ocrelizumab.[5]
- We looked at the effects of drug switching, and lowered and extended dosing as supported by European studies.[9]
- A secondary aim evaluated outcomes in African-American veterans with MS who are prescribed anti-CD20 drugs to manage their disease.
- Lastly, we aimed to highlight the economic relief of biosimilar drug vs brand drug use.

TABLE 1: DEMOGRAPHICS

Subjects with MS Rituximab PVVR group n = 36	
Age (mean years) [range]	47.86 [25-73]
Female (n)	17
Race (%): African American	81%
Caucasian	19%
MS Type (%):	
Relapse-Remitting	83%
Secondary Progressive	17%
Primary Progressive	0
Mean EDSS -stable [range]	3.3 [5-7]
Relapse (n) (reflects extended dosing)	1
B cell depletion*	81% no CD19/20 cells detected;
B cell repletion	19% with range 0.5%- 0.4% B cell depletion***
MRI	
GD + lesions	None
new lesions	None
T2 enlarging lesions	None
Dose 500mg (n) Rituximab and PVVR	184 total doses 0.99.9% had > one dose
Safety**	
Infection (grade 1)	UTI(14%);URI(2%);Herpetic(8%)
Infusion reaction	5% Mild transient itching; edema
Other (grade 2)	2% colitis; drug continued

Subjects with MS Ocrelizumab group n = 16	
Age (mean years) [range]	46.88 [30-69]
Female (n)	6
Race (%): African American	69%
Caucasian	31%
MS Type (%):	
Relapse-Remitting	75%
Secondary Progressive	12.5%
Primary Progressive	12.5%
Mean EDSS-stable [range]	3.5 [1.5-7.5]
Relapse (n)	2
B cell depletion*	94% no CD19/20 cells detected;
B cell repletion	6% had B cell detection ***
MRI	
GD + lesions	None
New lesions	None
T2 enlarging lesions	None
Dose 600mg (n)	16
Safety**	
Infection (grade 2)	N=2 requiring drug stop
Infusion reaction	6% mild transient itching/edema
Other	None

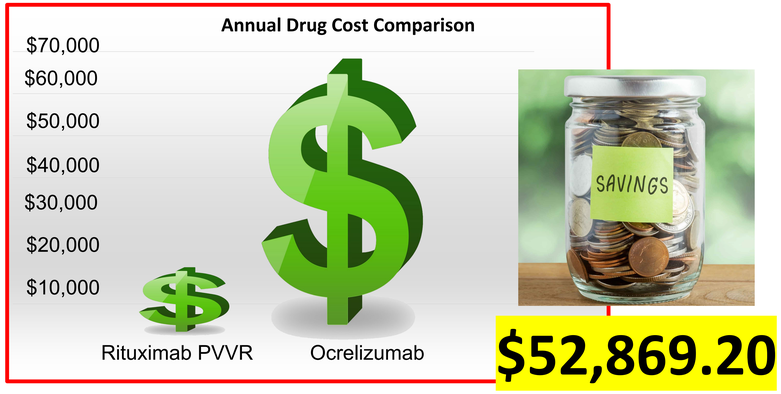
* "This test was developed, and its performance characteristics determined by the Pathology and Laboratory Medicine Service, Veterans Affairs Medical Center, Washington DC. It has not been cleared or approved by U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing. Per lab standard <0.4% is considered depleted.

**It is known that the CD20 epitope is overlapping for rituximab and ocrelizumab assuming similar efficacy yet, safety concerns emerge with the chimeric vs partially humanized nature of this class of anti CD20 drugs[5]. ***Ocrelizumab at 600mg/dose more fully suppressed CD 19/20 B cell compared to PVVR at 500mg/dose

RESULTS

- Our veteran cohort (n=52) was predominantly African American (77%) and men (44%) with median age of 47 years. The mean EDSS of 3.4 remained stable in both groups. MS disease subtype was predominantly relapsing-remitting (81%).
- Sixteen received Ocrelizumab at standard FDA approved dosing for a mean of 7.6 total lifetime doses.
- Nineteen veterans initialized biosimilar rituximab PVVR. Fifteen received brand-name rituximab followed by biosimilar rituximab PVVR 500mg* every six months for a mean of 2.27, 5.75 respective total doses.
- B cell depletion primarily remained at zero.
- B cell repletion occurred in those few with extended dosing schedules (>12 months) due to pregnancy, surgical delay, infection or choice.
- There were no safety or efficacy concerns when transitioning from brand rituximab or ocrelizumab to biosimilar rituximab PVVR. (Two switched from Ocrelizumab to PVVR; 15 switched from Rituximab to PVVR).
- Infection rates and infusion reactions were similar across both mAbs with more severe and persistent infections in the ocrelizumab cohort requiring discontinuation of drug.
- Gender, race, age and disease subtype had no influence on outcomes of relapse, MRI, B cells or safety parameters.

**Note on alternative rituximab dosing: After a one-time initial dose of 1000mg our cohort customarily received 500mg every six months*



METHODS

Design: Retrospective chart review of MS patients infused with highly efficacy anti-CD20 DMTs at the Washington DC VA Medical Center and MS Center of Excellence – East

The project was determined to be QI and not research by the DC VA Institutional Review Board.

We evaluated safety parameters, clinical and radiological outcomes and laboratory results for CD19/CD20 (B cell depletion and time to repletion) in 52 veterans with MS prescribed ocrelizumab and biosimilar rituximab PVVR. Demographic information was gathered on age, race, gender, and MS disease subtype.

DISCUSSION AND CLINICAL RELEVANCE

Discussion: The annual market cost of biosimilar rituximab PVVR* is less than one-fourth that of ocrelizumab ($15,130.80/1000mg[7]/ $68,000/600mg[6]). Biosimilar rituximab PVVR at doses 50% of usual was noninferior to ocrelizumab on all parameters of relapse, disease progression, MRI lesion activity and B cell depletion and repletion. Safety concerns were similar for both groups with infection most common. **Conclusions:** Drug cost are 80% of the overall economic burden of living with multiple sclerosis. The average annual pricing of biosimilar rituximab PVVR represents an annual savings of **$52,869.20 per patient.** Our results add data to the use of a biosimilar drug as a safe and highly efficacious DMT. Recognizing the disease stability offered by biosimilar rituximab in an African American cohort, with typically worse disease outcomes, reflects added confidence in biosimilar use. **Clinical Relevance**: Lowered and extended dosing adds to patient satisfaction and may contribute to safety and lifetime available doses. PVVR allows for individualizing treatment. Half-dose PVVR should be considered as an alternative to other anti-CD20 therapies as supported by European data.[9] Cost containment is a sustainable, equitable, obtainable value. **Limitations:** Biosimilar rituximab is not an MS FDA approved drug. Brand rituximab is confidently used off label. This QI project cannot be generalized to people with MS taking an anti-CD20 agent outside of the DC Veterans Affairs Medical Center. **Recommendations:** A call for further study of biosimilar DMT use in a broader population; more research on alternative DMT dosing of efficacy and safety; for all to be cognizant of the balance of resource stewardship, equity and positive outcomes for our patients.

Challenge: Utilizing choices thoughtfully is fundamental.

* Does not reflect Veterans Affairs negotiated prices

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