Test Definition: RAVU

Ravulizumab, S

Overview

Useful For

Assessing the response to ravulizumab therapy

Assessing the need for dose escalation

Evaluating the potential for dose de-escalation or discontinuation of therapy in remission states

Monitoring patients who need to be above a certain ravulizumab concentration in order to improve the odds of a clinical response for therapy optimization

This test is **not useful** as the sole basis for a diagnosis or treatment decisions.

Highlights

Therapeutic drug monitoring of ravulizumab may be useful when assessing response to therapy is difficult or when patients need to be above a certain therapeutic monoclonal antibody concentration in order to improve the odds of a clinical response for therapy optimization, including potential dose de-escalation or discontinuation of therapy in remission states.

Method Name

Liquid Chromatography-Tandem Mass Spectrometry, High Resolution Accurate Mass (LC-MS/MS HRAM)

NY State Available

Yes

Specimen

Specimen Type

Serum

Ordering Guidance

To screen test complement abnormalities in the alternative pathway, order RAVUM / Ravulizumab Complement Blockage Monitoring, Serum.

Specimen Required

Patient Preparation: Natalizumab or eculizumab must be discontinued at least 4 weeks prior to testing for ravulizumab quantitation in serum.

Preferred: Red top

Acceptable: Serum gel

Specimen Volume: 2.5 mL

Collection Instructions:

1. Draw blood immediately before next scheduled dose.

2. Centrifuge within 2 hours of collection.

Forms

If not ordering electronically, complete, print, and send a Coagulation Test Request (T753) with the specimen.

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	OK

Specimen Minimum Volume

1.1 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	28 days	
	Ambient	28 days	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

Ravulizumab (Ultomiris, Alexion Pharmaceuticals) is a humanized monoclonal IgG2/4 kappa antibody therapeutic

directed against the complement component 5 (C5). By association with C5, ravulizumab inhibits the terminal complement pathway through simultaneous blockade of the generation of the potent prothrombotic and proinflammatory molecule, C5a, and the formation of membrane attack complex initiator, C5b. Since all 3 arms of the complement cascade converge at the point of C5 activation, targeted by ravulizumab, this drug may have broad potential application and is being clinically evaluated in other disorders with complement over-activation. Since ravulizumab demonstrated noninferiority to eculizumab in clinical trials for both paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemalytic uremic syndrome (aHUS), there is likelihood of patients being moved from eculizumab to ravulizumab therapy. Ravulizumab is a longer-acting hybrid IgG2/IgG4 therapeutic monoclonal antibody (145 kDa). Its sequence is very similar to eculizumab (148 kDa), except for a 4 amino acid difference in the heavy chain of the molecule. Eculizumab binds to complement component C5 in the intravascular space and, after the resulting eculizumab-C5 complex is taken up by endothelial cells, it is degraded in the endosomes. In order to increase its half-life, two changes were made to ravulizumab: 2 amino acids substituted in the constant region give ravulizumab more affinity for the Brambell receptor (FcRn), which recycles IgG instead of degrading it. The other 2 amino acids changes are in the variable region of the heavy chain, changing the affinity of the Fab fraction for C5, making it possible for C5 to be released from ravulizumab before it is recycled, so that C5 is left alone inside the endosome to be degraded.

Eculizumab is administered as a standard (non-weight based) dose for approved conditions. Ravulizumab's key improvements over eculizumab include the longer half-life, leading to IV infusions every 8 weeks instead of every 2 weeks, along with a weight-based dosing schedule that further personalized therapy regimens. Some patients who persist with serum concentrations above therapeutic targets with complete complement blockade could benefit from dose de-escalation or prolonged infusion intervals, and visit the clinic for infusions less frequently than the FDA-label 2 weeks. Therapeutic drug monitoring of ravulizumab could result in cost-savings and improved quality of life if target therapeutic concentrations can be achieved with complete complement system blockage at less frequent dosing intervals.

Reference Values

Lower limit of quantitation=5.0 mcg/mL

>175 mcg/mL-Therapeutic concentration for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome

Interpretation

Target trough therapeutic concentrations (immediately before next infusion) of ravulizumab are expected to be above 175 mcg/mL for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Pharmacodynamic studies of complement blockage may also be recommended for patients undergoing therapy.

Cautions

Results must be interpreted within the clinical context of the patient. Patients in transition between eculizumab (ECULI / Eculizumab, Serum) and ravulizumab administration may have a skewed therapeutic level of the respective analytes reported under the relative orderable. Hence, measuring ravulizumab only after the loading dose scheme has been

completed and maintenance dose schedule is in place is suggested. Test results cannot be interpreted as absolute evidence for the presence or absence of malignant disease. This test should not form the sole basis for a diagnosis or treatment decisions.

Clinical Reference

1. Willrich MA, Murray DL, Barnidge DR, Ladwig PM, Snyder MR: Quantitation of infliximab using clonotypic peptides and selective reaction monitoring by LC-MS/MS. Int Immunopharmacol. 2015 Sep;28(1):513-520. doi: 10.1016/j.intimp.2015.07.007

2. Ladwig PM, Barnidge DR, Willrich MA: Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF Mass Spectrometry. J Am Soc Mass Spectrom. 2017 May;28(5):811-817. doi: 10.1007/s13361-016-1566-y

3. Ladwig PM, Barnidge DR, Willrich MA: Mass spectrometry approaches for identification and quantitation of therapeutic monoclonal antibodies in the clinical laboratory. Clin Vaccine Immunol. 2017 May 5;24(5). doi: 10.1128/CVI.00545-16

4. Sridharan M, Willrich MA, Go R: Personalized dosing of eculizumab using C5 functional activity and eculizumab level in complement-mediated thrombotic microangiopathy: A safe and cost-saving approach. Presented at XXVIII Congress of the International Society on Thrombosis and Haemostasis; July 12-14, 2020; Virtual ISTH 2020

5. Kulasekararaj AG, Hill A, Rottinghaus ST, et al: Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549. doi: 10.1182/blood-2018-09-876805

6. Stern RM, Connell NT: Ravulizumab: a novel C5 inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria. Ther Adv Hematol. 2019;10:2040620719874728. doi: 10.1177/2040620719874728

7. Alexion Pharmaceuticals. BLA 761108-S1 Multi-disciplinary review and evaluation: Ultomiris (ravulizumab-cwvz). FDA; April 2, 2019. Available at www.fda.gov/media/135113/download

Performance

Method Description

Ravulizumab is extracted from serum and measured by liquid chromatography (high-resolution accurate-mass) mass spectrometry.(Unpublished Mayo Method)

PDF Report

No

Specimen Retention Time

2 weeks

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

80299

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
RAVU	Ravulizumab, S	97184-6

Result ID	Reporting Name	LOINC®
609420	Ravulizumab, S	97184-6