MELLEN CENTER APPROACH: OFATUMUMAB

What is the clinical indication for ofatumumab?

Ofatumumab 20 mg monthly subcutaneous injection is FDA approved to treat relapsing forms of multiple sclerosis (MS) – clinically isolated syndrome, relapsing remitting multiple sclerosis, and active secondary progressive multiple sclerosis (patients who manifest secondary progression but continue to have disease activity, namely clinical relapses and/or new lesions on MRI). The benefit of ofatumumab in patients with primary progressive MS and secondary progressive MS without active inflammation has not been studied. At the Mellen Center, ofatumumab is used both for initial therapy as well as second-line therapy among those who have insufficiently responded to other therapies due to inadequate efficacy or adverse effects.

What is the mechanism of action of ofatumumab?

Ofatumumab is a fully humanized monoclonal anti-CD20 antibody constructed with recombinant DNA techniques and designed to selectively target CD20-expressing B-cells. Following cell surface binding, ofatumumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and apoptosis. The precise mechanisms through which ofatumumab exerts its therapeutic clinical effects in multiple sclerosis are not known but are likely mediated by a reduction in the number and function of CD20-expressing B-cells. Components of MS pathology potentially affected by this mechanism include reductions in: auto-antigen presentation, secretion of pro-inflammatory cytokines, production of autoantibodies, and formation of meningeal lymphoid follicle-like structures. It is likely that ofatumumab works very similarly to other anti-CD20 monoclonal antibodies.

How does the mechanism of action and route of administration of ofatumumab differ from other anti-CD20 monoclonal antibody therapies?

Ofatumumab is administered monthly via subcutaneous injection whereas ocrelizumab and rituximab are administered approximately every six months via intravenous infusion. Ofatumumab binds to a different CD20 epitope than that bound by rituximab and ocrelizumab. All three anti-CD20 therapies induce cell lysis in circulating B-cells. Compared to ocrelizumab, ofatumumab causes more cell-dependent cytotoxicity than complement-dependent cytotoxicity, although the clinical relevance of these mechanistic differences is unknown and likely minimal.

What are the kinetics of ofatumumab?

The average half-life of ofatumumab (pharmacokinetics) at steady state is approximately 16 days. However, the biologic effect of ofatumumab (pharmacodynamics) is much longer. Following drug discontinuation, more than 50% of patients recovered their B-cells between 24 and 36 weeks. Modeling and simulation predicts a median time to B-cell recovery of 40 weeks post treatment discontinuation.

Does ofatumumab have significant drug interactions?

Ofatumumab has no known significant drug-drug interactions. It does not share a common clearance pathway with drugs metabolized by the cytochrome P450 system or other drug metabolizing enzymes.

What are the major adverse events associated with ofatumumab?

The most common adverse events observed in the Phase III studies of ofatumumab were upper respiratory tract infections, urinary tract infections, headaches, injection-related reactions, and local injection site reactions. The majority of infections were mild and did not require inpatient hospitalization. In the Phase III studies, ofatumumab was compared to another MS disease modifying therapy, teriflunomide, which itself is associated with an increased rate of infections. The overall incidence of adverse events in the 30-month Phase III studies was similar between ofatumumab and teriflunomide. The Phase II trial compared ofatumumab to placebo and provides a clearer assessment of adverse events secondary to ofatumumab, although the study was a shorter duration (24 weeks). Ofatumumab-treated patients reported an increased incidence of injection-related reactions. This increase was observed over the 12 weeks following the first dose but not over the 12 weeks following the second dose. There has been an association with neoplasm with other B-cell therapies but this has not been observed with ofatumumab in the phase II or phase III clinical trials. Given the possibility for an injection-related reaction, we observe patients in clinic for their first injection of ofatumumab but do not pretreat with medications.

Safety data from phase III clinical studies (pooled data from ASCLEPIOS I and II)		
Side effect	Ofatumumab	Teriflunomide
Total infections	51.6%	52.7%
Upper respiratory tract infection	39%	38%
Urinary tract infection	10%	8%
Serious infections	2.5%	1.8%
Injection-related reactions	11%	6%
Headaches	13%	12%
Neoplasms	0.5%	0.4%
Safety data from phase II clinical study (MIRROR study)		
Side effect	Ofatumumab	Placebo
Total infections	27%	25%
Injection-related reactions (first dose)	52%	15%
Injection-related reactions (second dose)	13%	14%
Headaches	5%	6%

What effect on MS did the clinical trials of ofatumumab show?

The efficacy of ofatumumab was demonstrated in two double-blind, placebo-controlled, Phase 3 studies (ASCLEPIOS I and II) evaluating the efficacy and safety of ofatumumab vs teriflunomide (14 mg PO daily) in adult patients with RRMS. Below is a table summarizing the results from these studies:

	ASCLEPIOS I			**ASCLEPIOS II**		
	Ofatumumab	Teriflunomide	Risk reduction	Ofatumumab	Teriflunomide	Risk reduction
Annualized relapse rate	0.11 (0.09-0.14)	0.22 (0.18-0.26)	50.5% (<0.001)	0.10 (0.08-0.13)	0.25 (0.21 to 0.30)	58.5% (<0.001)
Confirmed disability progression at 3 and 6 months (pooled)	10.9%	15.0%	34.4% (0.002)	8.1%	12%	32.5% (0.012)
Confirmed disability improvement at 6 months	9.7%	8.2%	No difference	12.3%	8.1%	No difference
New gadolinium enhancing lesions on T1-weighted MRI (mean)	0.01 per scan (0.01-0.02)	0.45 per scan (0.36 to 0.58)	97.5% (<0.001)	0.03 per scan (0.02-0.05)	0.51 per scan (0.40 to 0.66)	93.8% (<0.001)
New or newly enlarged hyperintense lesions on T2-weighted MRI (mean)	0.72 per year	4.00 per year	82% (<0.001)	0.64 per year	4.15 per year	84.5% (<0.001)
Brain-volume change (mean percentage change)	-0.28%	-0.35%	No difference	-0.29%	-0.35%	No difference

How does the efficacy and safety of ofatumumab compare to ocrelizumab?

A direct comparison between ofatumumab and ocrelizumab is challenging because no head-to-head studies have been conducted. Additionally, the clinical trials used different comparators (teriflunomide was the comparator for ofatumumab while interferon β1a was the comparator for ocrelizumab). However, based upon individual clinical trial data, the effect of ofatumumab on clinical and MRI measures of MS appears more similar to ocrelizumab than different, and ofatumumab appears to have a comparable safety profile to ocrelizumab.

Is ofatumumab associated with progressive multifocal leukoencephalopathy (PML)?

To date (2022), no cases of PML have been reported for ofatumumab in MS. However, PML resulting in death occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) in which ofatumumab was administered at a higher dose than that used for MS

but for a shorter duration of treatment. Since rare cases of PML have been reported with other anti-CD20 monoclonal antibodies, it seems likely that rare cases of PML will be seen with ofatumumab, too. However, given the expected low rate of PML, at the Mellen Center we do not take into account JC virus serology when considering ofatumumab therapy and other anti-CD20 monoclonal antibodies and don't preclude patients with a positive JC virus serology from treatment with either ofatumumab or other anti-CD20 monoclonal antibodies.

Who should not receive ofatumumab?

Ofatumumab is contraindicated in patients with an active hepatitis B infection as it can cause worsening hepatitis. Consultation with hepatology is generally considered for non-active hepatitis B infection and other viral hepatitides. We screen for viral hepatitis using a remote hepatitis panel, which includes hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C antibody. Any patient with a positive hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody is referred to hepatology for further evaluation of viral hepatitis before initiating ofatumumab. Consultation with an immunologist before initiating treatment with ofatumumab may be considered in patients with low serum immunoglobulins at screening. In patients with frequent infections – particularly respiratory infections – the risk/benefit trade-off with ofatumumab may be unfavorable.

What testing is done before starting ofatumumab?

Baseline serum immunoglobulins, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, hepatitis C Ab, VZV Ab (to ensure adequate response to VZV), tuberculosis interferon gamma release assay (to screen for asymptomatic tuberculosis infection), CBC, and CMP should all be checked prior to initiating ofatumumab.

What monitoring is done during ofatumumab treatment?

We routinely check a CBC at least every 12 months in patients on therapy and a brain MRI at least every 12 months for efficacy monitoring. Post-marketing surveillance data demonstrated that IgG levels remain stable and IgM levels decline but on average remain above the lower limit of normal for up to 3.5 years after ofatumumab initiation. We have been monitoring quantitative serum immunoglobulins, although the clinical relevance of changes in these levels is unknown.

How is ofatumumab administered?

Ofatumumab is administered by subcutaneous injection. The initial loading dosing is 20 mg at weeks 0, 1, and 2. Starting at week 4, 20 mg is administered every month as a maintenance dose.

Is ofatumumab safe during pregnancy?

No definitive guidance is available on the effect of ofatumumab on pregnancy, but use during pregnancy and in women considering or attempting pregnancy is discouraged. Placental transmission to the fetus is unknown. We counsel woman to use effective contraceptive methods while on ofatumumab and wait at least 1-3 months (based on the half-life of the drug) since their

last ofatumumab dose before attempting conception. Data from other anti-CD20 monoclonal antibodies has shown that anti-CD20 administration during pregnancy leads to a transient B-cell depletion in the neonate.

Is ofatumumab safe while breast feeding?

There are no data on the presence of ofatumumab in breast milk. At the Mellen Center, we typically do not recommend ofatumumab treatment during breast feeding.

Which vaccines should a patient receive while on ofatumumab?

Live vaccines should be avoided for patients within 2 months of any ofatumumab injection and potentially longer based on prolonged B-cell reconstitution. Because ofatumumab may reduce the generation of new antibodies (as seen with other anti-CD20 monoclonal antibodies), patients should complete any required vaccines at least one month prior to initiating ofatumumab. Patients who receive vaccinations during ofatumumab therapy should be advised that the vaccine may be less effective than otherwise expected. Specifically regarding the COVID-19 vaccine, a decreased antibody response to the COVID-19 vaccine has been observed in MS patients receiving ocrelizumab. Given that ocrelizumab has a similar mechanism of action to ofatumumab, it seems likely that ofatumumab will attenuate the immune response to the COVID-19 vaccine, too. We advise any COVID-19 vaccine dose be given at least 14 days before and at least 14 days after injection of ofatumumab to improve the chances of a vaccine response.

Should we monitor CD19 counts in a patient on ocrelizumab?

We do not routinely monitor B-cell (CD19) counts in patients receiving ofatumumab or alter the administration schedule based on CD19 counts. The return of B-cells may inform the change to other therapies after ofatumumab, so checking CD19 counts may occasionally be useful to monitor the return of B-cells after cessation of ofatumumab treatment.

References

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