Tofacitinib (Xeljanz) for treatment of severe mast cell activation disease and/or severe mast cell activation syndrome (MCAS)

There is clinical experience by physicians that treat MCAS and 2 published case reports showing that tofacitinib (Xeljanz or long-acting Xeljanz XR) can be effective in drug-resist, aggressive mast cell activation disease/syndrome. This medication is currently approved for use in rheumatoid arthritis and psoriatic arthritis. It has been used in ulcerative colitis and is under review by the FDA for this indication.

Potential side effects from taking tofacitinib include increased risk for infections, cancer, and laboratory abnormalities. The following risks and advice are taken from the drug information provided by the drug company.

INFECTION RISK

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, we will need to interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use. Invasive fungal infections, including cryptococcosis and pneumocystosis have been reported.

The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Avoid use of XELJANZ/XELJANZ XR in patients with an active, serious infection, including localized infections. Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infection.

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was observed in clinical studies with XELJANZ. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ/XELJANZ XR. The risk of herpes zoster is increased in patients treated with XELJANZ/XELJANZ XR and appears to be higher in patients treated with XELJANZ in Japan and Korea.

MALIGNANCY RISK

Lymphoma and other malignancies have been observed in patients treated with XELJANZ.

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer

(NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy.

In the 7 controlled rheumatoid arthritis clinical studies, 11 solid cancers and 1 lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without disease-modifying antirheumatic drugs (DMARD), compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ. In the 2 controlled Phase 3 clinical trials in patients with active psoriatic arthritis, there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus nonbiologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus nonbiologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus nonbiologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic arthritis patients treated with XELJANZ. In Phase 2B controlled dose-ranging trials in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus–associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine. Other malignancies were observed in clinical studies and the post-marketing setting including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in XELJANZ clinical trials, although the role of JAK inhibition is not known. XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis).

LABORATORY ABNORMALITIES

Lymphocyte Abnormalities

Treatment with XELJANZ was associated with initial lymphocytosis at 1 month of exposure followed by a gradual decrease in mean lymphocyte counts of approximately 10% during 12 months of therapy. Counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections

Treatment with XELJANZ was associated with initial lymphocytosis at 1 month of exposure followed by a gradual decrease in mean lymphocyte counts of approximately 10% during 12 months of therapy. Counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a count less than 500 cells/mm^3. In patients who develop a confirmed absolute

lymphocyte count less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Monitor lymphocyte counts at baseline and every 3 months thereafter.

Neutropenia

Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with an absolute neutrophil count less than 1000 cells/mm^3. For patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ/XELJANZ XR dosing until absolute neutrophil count is greater than or equal to 1000 cells/mm^3. In patients who develop an absolute neutrophil count less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment. Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Liver Enzyme Elevations

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be stopped. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

Lipid Elevations

Treatment with XELJANZ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. Assess lipid parameters approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy, and manage patients according to clinical guidelines for the management of hyperlipidemia.

Consent:

I have read the above information and wish to take Tofacitinib (Xeljanz) therapy. I will comply with lab monitoring.** I understand and accept the risks and understand that this therapy is used in cases of mast cell diseases where the symptoms have not responding to numerous treatments and the quality of life is so impaired that innovative therapy is required. I have been

given this form in advance of taking the medication and was allowed to read it and ask my physician questions regarding this medication.

Signature/date: _____ _____

> **Labs: Baseline TB blood test and chest x-ray, CBC and CMP. During therapy have CBC (complete blood count) weekly for the first month, biweekly for the second month, and monthly; CMP (complete metabolic panel) monthly.
> Dermatology evaluation: yearly skin examination is recommended for patients who are at increased risk for skin cancer.

References:

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Supplementary information from the article by Dr. Afrin on tofacitinib and MCAS:

Mast cell (MC) activation syndrome (MCAS) is a collection of illnesses of inappropriate MC activation with little to no neoplastic MC proliferation, distinguishing it from mastocytosis. MCAS presents as chronic, generally inflammatory multisystem polymorbidity likely driven in most by heterogeneous patterns of constitutively activating mutations in MC regulatory elements, posing challenges for identifying optimal mutation-targeted treatment in individual patients. Targeting commonly affected downstream effectors may yield clinical benefit independent of upstream mutational profile. For example, both activated KIT and numerous cytokine receptors activate the Janus kinases (JAKs). Thus, JAK-inhibiting therapies may be useful against the downstream inflammatory effects of MCAS. The oral JAK1/JAK3 inhibitor, tofacitinib, is currently approved for rheumatoid arthritis and is in clinical trials for other chronic inflammatory disorders. Herein, we report two patients with MCAS who rapidly gained substantial symptomatic response to tofacitinib. Their improvement suggests need for further evaluation of this class of drugs in MCAS treatment.

Case 1

A 55 year old businesswoman sought evaluation in July 2014 for the MCAS she had come to suspect was at the root of her chronic multisystem polymorbidity of generally inflammatory theme. Other than consistently lagging on growth curves, she could not recall any significant

childhood health issues. Menarche came at age 10, and chronic multisystem unwellness began at 12 with acute but relatively brief attacks of abdominal pain of severity sufficient to require emergency evaluation each time, albeit always unrevealing as to a cause; a diagnosis of "menstrual cramping" was sometimes made. At age 20 she suffered extensive left leg traumatic fractures in a motor vehicle accident, requiring a year for complete recovery. At age 22 she was non-specifically unwell throughout her first pregnancy which was otherwise unremarkable, but six weeks after delivery she noticed cervical adenopathy and soon was diagnosed with Stage II-B Hodgkin's lymphoma. She achieved complete remission with mechlorethamine, vincristine, procarbazine, and prednisone (aborted after 8 of a planned 22 cycles due to thrombocytopenia, and prednisone was omitted soon after initiation of treatment due to mania) followed by adjuvant radiotherapy to bilateral cervical and mantle fields. Her second and final pregnancy at 28 was complicated only by a right ureteral stone requiring removal. At 30, when she was under much family and work stress, she began suffering sporadic episodes of diarrhea that proved to be medication-refractory, and she also developed chronic diffuse body aching and exhaustion, requiring a two-hour nap each day after work. Absent any other apparent cause, all of these symptoms were attributed to her prior lymphoma treatment. Uterine prolapse was diagnosed at age 32. More stress ensued at age 34 due to a serious family medical issue, and she also anaphylaxed at this time to a fire ant bite even though she had been bitten many times previously by fire ants and had never previously had any significant reaction. She underwent six months of immunotherapy for a fire-ant allergy newly documented at that time.

She continued to manifest waxing/waning periods of malaise, aching, and fatigue. Additional series of immunotherapy treatments were unhelpful. Fibromyalgia was diagnosed. All of these symptoms continued in a fluctuating fashion, with flares increasing in intensity and frequency over time. Prophylactic appendectomy was performed at age 39 during otherwise unrevealing exploratory laparotomy for another episode of acute severe abdominal pain. Colorectal and bladder prolapse were diagnosed at age 46. At age 54 she became aware her symptoms fit the profile of mast cell activation disease (MCAD). Limited testing for such was negative, but she began taking several MCAD-directed medications and quickly began feeling significantly better. All of her symptoms persisted, but to a lesser degree of intensity and with less frequency. Also, vague left neck nodularity that had persisted since the bout with lymphoma completely resolved soon after beginning MCAD-directed medication. In March 2014 she received a cortisol injection in the left knee following joint replacement surgery, but this caused severe depression requiring a month for recovery, and then, because of poor healing, a revision to the surgery was required in May 2014, a few days after which she had to be rehospitalized for an acute flare of nausea, vomiting, diarrhea, bloating, and severe hypertension (blood pressure 200/140), all of which improved with histamine H_1 and H_2 receptor antagonists. She was felt to have developed a non-ST-wave endomyocardial infarction (though coronary artery catheterization found no partial or complete occlusion, suggesting the possibility of Kounis syndrome (allergic vasospastic angina)) and was briefly on heparin without bleeding and tolerated low-dose aspirin well.

She also had been diagnosed in July 2014 with seronegative, erosive RA (and possibly also Ehlers Danlos Syndrome (suspected type III, hypermobility)). She was immediately started on leflunomide (the only disease-modifying anti-rheumatic drug tried prior to tofacitinib), but no improvement was seen.

The symptoms she endorsed on a full review of systems at the initial evaluation for MCAS in July 2014 are listed in Table 1.

Family history was notable for her father dying of complications from Wegener's granulomatosis (WG) at age 67 (note he also had cardiac disease from an early age and had a completely transfusion-dependent pure red cell aplasia for at least several months prior to his death, and this was blamed on cyclophosphamide used to treat WG), severe acquired idiopathic leukopenia in a paternal aunt, and a brother with multiple sclerosis. The patient admitted to a minimal, intermittent smoking history during assorted stressful periods in the past but permanently quit at age 39. She had long reacted to alcohol with hypertension and flushing helped by Benadryl. She denied illegal substance use.

Other than a tired, aged general appearance, mild tachycardia, and mild dermatographism, physical examination was unremarkable.

Review of laboratory data showed chronic leukopenia for many years after lymphoma treatment that had finally returned to normal around age 50, the same time that a slow but steady rise in hemoglobin and hematocrit first emerged.   Occasional minimal relative monocytosis became evident. Screenings for Lyme disease and alpha-1-antitrypsin deficiency were negative. Also at 50, non-contrasted sinus CT revealed only a deviated nasal septum, brain MRI (contrasted and non-contrasted) was normal, and anti-nuclear antigen (ANA) was negative. At age 51 gallbladder ultrasound was normal, esophagogastroduodenoscopy found only mild erythematous inflammation in the stomach (blind biopsies showed only mild chronic inactive H. pylori-negative gastritis), and colonoscopy revealed only sigmoid diverticulosis and non-bleeding internal hemorrhoids. At age 53 there was an isolated finding on the leukocyte differential of 5% atypical lymphocytes, and an echocardiogram was essentially normal. Contrasted chest/abdomen/pelvis tomography at age 54 showed only mild diffuse fatty liver infiltration and a 1.6 cm left hepatic lobe hemangioma. In September 2013 (age 54), serum protein electrophoresis was normal and plasma histamine, rheumatoid factor, and ANA were all undetectable, but hepatic transaminases were minimally elevated. In January 2014 (age 55), left knee radiography showed severe osteoarthritis and a distal femoral bone cyst. In February 2014 bone scan showed mild changes consistent with prior fractures and scattered degenerative change. Resected left knee bone in March 2014 showed only marked degenerative changes consistent with osteoarthritis and, on Giemsa and tryptase staining, a few scattered mast cells. Right tibia/fibula radiography in March 2014 showed scattered sclerotic densities. At re-hospitalization in May 2014, hemoglobin was 15.2 g/dl, echocardiogram remained normal, and C-reactive peptide was quite high at 7.5 (normal < 1.0). In August 2013, hemoglobin was 14.3 g/dl, MCV was 90 fL, serum tryptase was normal (4 ng/ml, normal < 11), plasma histamine was normal at an undetectable level, serum chromogranin A was slightly low, and KIT-D816V mutation analysis on peripheral blood was negative. In May 2014 skeletal imaging showing diffuse osteopenia but also some patches of osteosclerosis and bilateral finger joint changes consistent with degenerative joint disease and erosive inflammatory arthropathy consistent with RA. In June 2014 a complete blood count was again normal in spite of a low serum vitamin B12 level at 120 pg/ml (normal 200-1100), thyroid function tests were unremarkable, HLA-B27 and anti-cyclic citrullinated peptide antibodies and anti-neutrophil-cytoplasmic antibodies were negative, and levels of quantitative immunoglobulins G, A, M, and E were normal.   Also unremarkable in June 2014 were an EBV early antigen study, complement C3 and C4 levels, cryoglobulin screen, creatine kinase, and an extractable nuclear antigen panel.

Mast cell activation disease (MCAD) – more likely mast cell activation syndrome (MCAS) than systemic mastocytosis (SM) given the normal serum tryptase – was suspected to be the unifying diagnosis. JAK2 mutation analysis and 24-hour urinary 5-HIAA testing were normal.

Plasma histamine was mildly elevated (9 nmol/L, normal 0-8) and 24-hour urinary prostaglandin D_2 was significantly elevated at 437 ng/24h (normal 100-280).

She was diagnosed with MCAS. [1] She was already taking cetirizine, famotidine, cromolyn, ketotifen, diphenhydramine, montelukast, and thyroid replacement. Increases in ketotifen and montelukast were recommended as initial maneuvers to try, but before such trials could be pursued, her rheumatologist started her on a trial of tofacitinib at 5 mg twice daily in October 2014 (age 56). She noticed improvement in multiple symptoms by the end of the first week, and by the end of the second week she felt all of her symptoms had virtually completely remitted, including her episodes of post-prandial acute abdominal distention. She was able to significantly decrease her other MC-directed medications (e.g., decreasing ketotifen from 4 mg thrice daily to 2 mg twice daily). She found that an occasional extra dose of tofacitinib 5 mg at the time of symptomatic flares (roughly twice a year) reliably, quickly settled these episodes. In May 2016, she switched to extended-release tofacitinib 11 mg once daily, immediately reporting even more "improved stability" and further improvement in the range of foods she can tolerate. The only toxicity to emerge was abdominal pruritus with the extended-release formulation, suggesting reaction to an excipient in that formulation which is not present in the prior formulation. Her virtually complete symptomatic remission has continued uninterrupted for 29 months of tofacitinib use as of the time of this writing.

Case 2

The 29 year old daughter of Case 1 sought evaluation in June 2015 for the MCAS she, too, had come to suspect was at the root of her chronic multisystem polymorbidity of generally inflammatory theme. She was born with low APGARs of 2 and 7 and hypoxemia due to the cord being wrapped around her neck. She was persistently colicky throughout infancy and would frequently cry for extended spells for no apparent reason, then suddenly stopping immediately after producing a loose stool. Her stools continued to be loose throughout toddlerhood. She suffered many idiopathic rashes in toddlerhood. Chest pain emerged at age 7 years, but evaluation, including a Holter monitor, was unrevealing and she was diagnosed with exercise-induced asthma. Chronic temporomandibular joint dysfunction also emerged at 7. She exhibited poor/slow healing ever since early childhood. She suffered frequent severe otitis in one ear or the other throughout childhood. Her blood pressure was always borderline hypotensive. She suffered marked chronic fatigue throughout childhood. She was diagnosed with attention deficit hyperactivity disorder at 7, but this diagnosis was then thought, many years later, to be incorrect. She suffered much unexplained nausea, vomiting, and chronic malaise throughout childhood. Loose stools in toddlerhood gave way to chronic severe constipation beginning in early childhood. A low-grade fever was frequently present since early in childhood. She also suffered many fractures throughout childhood from trivial traumas. She recalled "always" suffering chronic diffusely migratory bone pain to her earliest memories. At age 8 she was evaluated with an intravenous pyelogram for months of "kidney pain," discovering double ureters on the right but no other cause. She was chronically sickly while growing up. Menarche came at 14 and was unremarkable. At 18 she suffered syncope four times within a two-month period, each time triggered by a sudden environmental temperature change. In the last such episode, she also suffered a pseudo-seizure. Her menstrual periods became irregular at this time. Her first pregnancy, at 19, was accompanied by hyperemesis gravidarum for the entire gestation. She also was constantly presyncopal throughout the pregnancy and had to remain in bed for most of the pregnancy. Delivery was induced early due to placental detachment. Following the delivery her periods became regular again but far more painful, erratic in duration, and with menorrhagia. On multiple emergent evaluations, her platelet count was 80,000-100,000 for no apparent reason. At 23 she suffered an idiopathic

three-week spell of severe nausea and vomiting, occasioning her first esophagogastroduodenoscopy (EGD) and a gastric transit time study which showed slow transit. Hepatobiliary iminodiacetic acid scan showed half the normal bile ejection. She began suffering repeated, roughly year-long episodes, with some intervening respites, of "constant vomiting," for which dronabinol, begun in April 2015, finally brought partial relief. Other problems for most of her 20s included an odd facial and perineal cystic dermatosis of unclear etiology, plus she continued to often be presyncopal upon exposure to significant environmental temperature changes. Exposure to hot water (e.g., a shower) reliably turned her skin "totally red." She long suffered presyncopal episodes in supermarkets upon transitioning from hot to cold areas; she would then proceed to the pharmaceutical aisle, open and drink a bottle of liquid diphenhydramine, and quickly feels better. Pap smear at 23 was abnormal, leading to a cervical freezing procedure; she also was found to have estrogen excess and absent progesterone. She had never tolerated alcohol, with just a tiny drink causing a syndrome of nausea, vomiting, and fever typically lasting three days. Diffuse joint laxity and subluxations were noted for many years, and at 28 she was diagnosed with EDS3. She reported many years of urinary and fecal frequency. She suffered a left kidney stone at 28. After her mother's diagnosis of MCAS, she came to suspect she herself also had this.

The symptoms she endorsed on a full review of systems at the initial evaluation for MCAS in June 2015 are listed in Table 1.

She smoked up to a half pack of cigarettes per day from 14 until quitting at 27. She denied any history of illegal substance use.

She was taking fexofenadine 180 mg once daily, cetirizine 10 mg once daily, famotidine 20 mg twice daily, diphenhydramine as needed, alprazolam 0.5-1 mg twice daily, oral cromolyn 300 mg four times daily, compounded oral ketotifen 2 mg twice daily, dronabinol 2.5 mg thrice daily, an epinephrine autoinjector as needed for anaphylaxis, and a daily oral contraceptive. She reported her current allergies as only anaphylaxis to bee stings and rash to sulfa.

Exam found a trim woman somewhat burdened with facial acne and sparsely scattered folliculitis. There was minimal scattered bruising, sparsely scattered small patches of macular erythematous rash, and paresthesias in the bilateral feet. Mildly bright dermatographism (but not Darier's sign) soon emerged on light scratch test and was fully sustained 10 minutes later.

Lab testing was significant for plasma heparin level of 0.07 anti-Factor Xa units/ml (upper normal 0.02 [2]), serum chromogranin A (160 ng/ml, normal 0-95), and (3) slightly increased mast cells by CD117 staining (27/hpf in both gastric and colonic biopsies, upper normal generally considered 20/hpf [3]).

She was diagnosed with MCAS. [1] Other than hydroxyzine 10 mg, which proved modestly helpful on an as-needed basis, due to social circumstances she was unable to immediately implement any of the several therapies initially suggested to her. However, in June 2016 she was able to begin immediate-release tofacitinib 5 mg twice daily (the 11 mg extended-release formulation was sought but not covered by her insurance). As had been the case in her mother, within the first few days she started feeling significantly better with increased energy and alertness, better sleep, reduced acne and folliculitis (present since 22), and decreased diarrhea. She was able to reduce her oral cromolyn from 300 mg four times daily to 200 mg four times daily. Other symptoms continued without improvement. In early January 2017, with a change of insurance, she was able to access the extended-release formulation and

immediately switched to it. Again as had been the case in her mother, she saw almost immediate further improvement with increased energy, reduced (but still constant) joint pain, and better sleep without nightly early waking with joint pain. Formerly daily nausea and diarrhea resolved. Formerly twice weekly headaches resolved. Folliculitis reduced further. At the time of this writing the patient's improvements on tofacitinib have been sustained eight months. No new disease symptoms have emerged since beginning tofacitinib, and no toxicities were noted from either formulation of tofacitinib.

References

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