Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement 3 Appendix

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eBox. All Eligibility Criteria for Enrollment in the FAST Uveitis Randomized Clinical Trial

Inclusion Criteria (All must be met)

- 16 years of age or older
- History of noninfectious intermediate, anterior and intermediate, posterior or panuveitis in at least one eye
- Active inflammation within the last 180 days, defined by the presence of **any of the following** (in at least one eye) according to SUN criteria and the NEI vitreous haze grading scale:
  - ≥ 2+ anterior chamber cells and/or
  - ≥ 2+ vitreous haze and/or
  - active retinal or choroidal inflammation
- Active inflammation in at least one eye at enrollment, defined by **any of the following**:
  - ≥ 1+ anterior chamber cells and/or
  - ≥ 1+ vitreous haze and/or
  - active retinal/choroidal inflammation (bullous serous retinal detachment qualifies if choroidal thickening)
- **At least one** of the following criteria must be met before or at enrollment:
  - 1.) Active inflammation after 4 weeks of high-dose (1mg/kg prednisone equivalent) oral corticosteroid treatment
  - 2.) Treatment with oral corticosteroids resulting in a reduction of inflammation, followed by an increase in inflammation (of at least 1 grade in anterior chamber cells or vitreous haze or a change of non-active to active retinal/choroidal lesions) when corticosteroid is tapered, in the 180 days prior to enrollment
  - 3.) Treatment with ≥10mg/day oral prednisone or equivalent over at least the past 90 days prior to enrollment
  - 4.) Active inflammation after long-acting corticosteroid injection 4 weeks to 180 days prior to enrollment
  - 5.) One of the following uveitic conditions necessitating corticosteroid-sparing immunosuppressive treatment[4]:
    - Behcet's disease with posterior segment involvement
    - Multifocal choroiditis with panuveitis
    - Serpiginous choroidopathy
    - Birdshot retinochoroidopathy
    - Diffuse retinal vasculitis
    - Severe Vogt-Koyanagi-Harada syndrome (VKH) (for example: acute VKH that has been active for at least 4 weeks, or VKH with bullous serous retinal detachments and/or choroidal detachments with other signs of ocular inflammation)
    - Sympathetic ophthalmia
  - 6.) Other conditions necessitating corticosteroid-sparing immunosuppressive therapy determined on a case-by-case basis.
- Willingness to start corticosteroid treatment at 1mg/kg or 60mg a day of prednisone, whichever is less (starting at a lower dose is acceptable if patient has known tolerability issues)
- Willingness to limit alcohol consumption (American College of Rheumatology recommendation is 2 drinks per month or less)
- Willingness to use an acceptable method of contraception during the study period (i.e. pharmacologics, devices, barrier methods) or abstinence.

Exclusion Criteria (Any one excludes patient)

- Any infectious cause of uveitis
- Prior immunosuppressive therapy other than corticosteroids in the past 12 months
- Prior intolerability or safety issues with methotrexate or mycophenolate mofetil
- Prior failure to control ocular or other inflammation using methotrexate or mycophenolate mofetil
- Prior biologic therapy at any time
- < 16 years of age at enrollment
- Media opacity (such as cataract and/or corneal scar) and/or extensive posterior synechiae such that examination of the posterior segment is not possible in both eyes
- Chronic hypotony (IOP < 5 mm Hg for > 3 months) in both eyes
- Periocular or intravitreal corticosteroid injection in the past 4 weeks
- Fluocinolone acetonide implant in either eye in < 3 years
- Intraocular surgery in < 30 days, or planned surgery within the next 180 days
- Best spectacle-corrected visual acuity of hand motion or worse in better eye
- Planning to conceive during the study period, pregnant or breast-feeding (blood or urine pregnancy test for all females, excluding those who are post-menopausal is mandatory within 4 weeks prior to enrollment)
- History of cancer (If a patient has a history of non-melanoma skin cancer they can still be considered for inclusion in this study, provided it is not currently active).
- Systemic autoimmune disease or ocular condition (besides uveitis) anticipated to dictate treatment course
- Abnormal CBC (≤ 2,500 white blood cells and/or ≤ 75,000 platelets and/or ≤9 hemoglobin) within 4 weeks prior to enrollment*
- Abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 2 times the upper limit of normal for the lab and/or creatinine ≥ 1.5 within 4 weeks prior to enrollment
- Evidence of active tuberculosis, HIV infection, syphilis, or hepatitis B or C (patients must have a tuberculin skin test, or interferon-gamma release assay, a chest radiograph, RPR/VDRL, FTA-ABS, or other treponemal tests, Hepatitis B surface antigen and Hepatitis C antibody tests within 90 days prior to enrollment)

eTable 1. Definitions of Serious and Nonserious Adverse Events

	Non-Serious	Serious
Ocular Adverse Events		
Ocular Hypertension	≥ 24 mm Hg	Surgery required (laser or incisional)
Glaucoma	Suspect or confirmed diagnosis of glaucomatous optic nerve damage	Confirmed diagnosis with > 3 lines of vision loss or decrease in mean deviation (MD) by 10 dB or more
Hypotony	IOP < 5 mm Hg without retinal or choroidal folds, elevation of optic nerve head, suprachoroidal effusions or hemorrhage, or corneal striae associated	IOP < 5 mm Hg with structural changes or ocular changes indicative of hypotony such as retinal or choroidal folds, elevation of optic nerve head, suprachoroidal effusions or hemorrhage, or corneal striae associated
Cataract	Visually significant cataract / cataract surgery indicated	Not applicable (n/a)
Vitreous hemorrhage	Peripheral and/or central vitreous hemorrhage	n/a
Endophthalmitis	n/a	Any occurrence is a serious adverse event
Retinal detachment (excluding serous)	n/a	Any occurrence is a serious adverse event
Other ocular event	Describe	Condition resulting in permanent vision loss. Describe.
Laboratory Abnormalities		
Leukocytes	>1,000 and <2,500/μL lasting less than 28 days	< 2,500/μL for at least 28 days or ≤ 1,000/μL
Platelets	20,000 to 75,000/μL lasting less than 28 days	<75,000/μL for at least 28 days or < 20,000/μL
Hemoglobin	≥ 6.5 to < 9 g/dL lasting less than 28 days	< 9 g/dL for at least 28 days or < 6.5 g/dL
SGOT (AST) or SGPT (ALT)	2 to 5 times the upper limit of normal lasting less than 28 days	2 to 5 times the upper limit of normal for at least 28 days or > 5 times the upper limit of normal
Creatinine	≥ 1.5 to < 2 mg/dL lasting less than 28 days	≥ 1.5 to < 2 mg/dL for at least 28 days or ≥ 2 mg/dL
Systemic Adverse Events		
Nausea	Any nausea	Severe discomfort, minimal food intake for 3 or more days **or** at least a 2.5 kg weight loss resulting from nausea
Vomiting	Any vomiting	Vomiting all food or fluids in 24 hours or orthostatic hypotension or at least a 2.5 kg weight loss resulting from vomiting

	Non-Serious	**Serious**
Diarrhea	Any diarrhea	Severe, bloody diarrhea or 8-9 loose stools in 24 hours or orthostatic hypotension **or** at least a 2.5 kg weight loss resulting from diarrhea
Dyspnea	Breathlessness on significant exertion **or** breathlessness at normal level of activity	Breathlessness at rest
Headache	Moderate, non-narcotic analgesic therapy required	Severe, requires narcotic therapy
Fatigue	Self-reported fatigue	Normal activity reduced >50%; cannot work or unable to care for self
Fever for 12 hours	> 100.6 to 103°F/39.5°C	≥ 103°F/39.5°C
Muscle weakness	Subjective weakness, no objective symptoms **or** mild objective weakness, no decrease in function	Objective weakness, function limited, or worse
Mood changes	Self-reported mood changes or psychiatric diagnosis not requiring medical therapy	Psychiatric diagnosis requiring medical treatment or hospitalization
Cardiac function	Mild congestive heart failure (CHF) or arrhythmia not requiring treatment or moderate CHF or worse, arrhythmia requiring treatment, stable angina	Unstable angina, severe CHF, myocardial infarction, or arrhythmia requiring hospitalization
Neurologic function	Numbness or tingling	Total loss sensation
Allergic reaction	Pruritis without rash or erythema or localized urticaria, diffuse maculopapular rash, dry desquamation	Generalized urticaria, angioedema or worse, vesiculation, moist desquamation, ulceration up to and including: exfoliative dermatitis; mucous membrane involvement; or Stevens-Johnson Syndrome, or erythema multiforme, or necrosis requiring surgery
Systemic infection	Any systemic infection.	Systemic infection requiring hospitalization or any infection lasting for more than 28 days
Other systemic	No treatment required and no limitations or mild impairment of usual activities	Vigorous treatment, hospitalization usually required, immediate risk of death
Seizure	n/a	Any occurrence is a serious adverse event
Cancer	n/a	Any occurrence is a serious adverse event
Congenital Anomaly/Birth Defect	n/a	Any occurrence is a serious adverse event
Disability or Permanent Damage	n/a	Any occurrence is a serious adverse event

	Non-Serious	Serious
Hospitalization	n/a	Any occurrence is a serious adverse event
Life-threatening event	n/a	Any occurrence is a serious adverse event
Required intervention to prevent permanent impairment/damage	n/a	Any occurrence is a serious adverse event
Death	n/a	Any occurrence is a serious adverse event
Other serious (important medical events)	n/a	Any occurrence is a serious adverse event

eTable 2. Enrollment Totals by Center

Center	Enrolled
	N (%)
Madurai	65 (30%)
Pondicherry	36 (17%)
Coimbatore	35 (16%)
San Francisco	34 (16%)
Melbourne	21 (10%)
Portland	11 (5%)
Riyadh	9 (4%)
Mexico City	3 (1%)
Chicago	2 (1%)
Total	216

eTable 3. Dose Reduction Guidelines for Study Medication

	Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Reduction Level I	Methotrexate	10mg BID						
	Mycophenolate mofetil	1g BID	1g BID	1g BID	1g BID	1g BID	1g BID	1g BID
Reduction Level II	Methotrexate	7.5mg BID						
	Mycophenolate mofetil	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID

eTable 4. Six-Month Patient-Reported Other Ocular Adverse Events

Type	Methotrexate (N=107)	Mycophenolate Mofetil (N=108)
	Number of Patients Reporting at Least One Event (%)	Number of Patients[a] Reporting at Least One Event (%)
Decrease in vision/defective vision	9 (8.4)	19 (17.6)
Eye irritation/burning/itching	3 (2.8)	4 (3.7)
Eye pain	9 (8.4)	4 (3.7)
Eye floaters	5 (4.7)	5 (4.7)
Eye redness	5 (4.7)	4 (3.7)
Eye flashes	3 (2.8)	2 (1.9)
Eye strain/perceived pressure changes	5 (4.7)	2 (1.9)
Photophobia/glare	3 (2.8)	2 (1.9)
Other ocular issue	7 (6.5)	4 (3.7)
Any ocular adverse event	30 (28.0)	33 (30.6)

[a]Out of 107 patients who received methotrexate and 108 patients who received mycophenolate mofetil (1 patient never received mycophenolate mofetil due to medical contraindication discovered post-randomization

eTable 5. Six-Month Patient-Reported Mood-Related Adverse Events

Type	Methotrexate (N=107)	Mycophenolate Mofetil (N=108)
	Number of Patients Reporting at Least One Event (%)	Number of Patients[a] Reporting at Least One Event (%)
Irritability	1 (0.9)	1 (0.9)
Anxiety	12 (11.2)	9 (8.3)
Depression	10 (9.3)	5 (4.6)
Frustration	5 (4.7)	5 (4.6)
High energy/giddiness	3 (2.8)	4 (3.7)
Difficulty concentrating/confusion	5 (4.7)	4 (3.7)
Apathy	2 (1.9)	1 (0.9)
Mood variability	7 (6.5)	2 (1.9)
Other mood issue	2 (1.9)	3 (2.8)
Any mood-related adverse event	22 (20.6)	19 (17.6)

[a]Out of 107 patients who received methotrexate and 108 patients who received mycophenolate mofetil (1 patient never received mycophenolate mofetil due to medical contraindication discovered post-randomization)

eTable 6. Six-Month Patient-Reported Other Systemic Adverse Events

Type	Methotrexate (N=107)	Mycophenolate Mofetil (N=108)
	Number of Patients Reporting at Least One Event (%)	Number of Patients[a] Reporting at Least One Event (%)
Muscle aches and pains/joint pain/neck pain/cramping	14 (13.1)	16 (14.8)
Swelling/ankle edema/facial puffiness	12 (11.2)	11 (10.2)
Weight gain/appetite change	0 (0.0)	0 (0.0)
Rash/skin changes/tinea	0 (0.0)	0 (0.0)
Stomach pain/heart burn/acid reflux	13 (12.1)	9 (8.3)
Dizziness	16 (15.0)	9 (8.3)
Sleep apnea/trouble sleeping/nightmares	14 (13.1)	11 (10.2)
Abdominal bloating	8 (7.5)	4 (3.7)
Shaky hands/shaky body/tremors	8 (7.5)	3 (2.8)
Cold/flu	6 (5.6)	2 (1.9)
Temperature changes	8 (7.5)	5 (4.6)
Constipation/change in bowel movements	16 (15.0)	17 (15.7)
Heart palpitations	4 (3.7)	4 (3.7)
Chest pain	2 (1.9)	3 (2.8)
Increased blood sugar	3 (2.8)	4 (3.7)
Tinnitus	5 (4.7)	5 (4.6)
Cold sore/mouth sore	2 (1.9)	1 (0.9)
Sinus/chest congestion	4 (3.7)	2 (1.9)
Chicken pox/zoster	6 (5.6)	1 (0.9)
Genital infection/discharge/sores	4 (3.7)	6 (5.6)
Sore throat/cough	1 (0.9)	3 (2.8)
Delayed healing	4 (3.7)	0 (0.0)
Numbness/tingling	13 (12.1)	11 (10.2)
Frequent urination	2 (1.9)	2 (1.9)
Other systemic	3 (2.8)	2 (1.9)
Any systemic adverse event	59 (55.1)	55 (50.9)

[a]Out of 107 patients who received methotrexate and 108 patients who received mycophenolate mofetil (1 patient never received mycophenolate mofetil due to medical contraindication discovered post-randomization)

eTable 7. Tests of Homogeneity of Effect for the 6-Month Primary Outcome

Primary Model[a] with Interaction Term	*P* value[b]
India[c]	.15
Site[c]	.20
Country[c]	.45
[a]6-month primary outcome logistic regression model with treatment group as a fixed effect and an interaction term	
[b]*P* value of the interaction term	
[c]Fixed effect	

eTable 8. Six- to 12-Month Adverse Events from a RCT Comparing Methotrexate and Mycophenolate Mofetil for Noninfectious Uveitis in Patients Continuing on Treatment after Treatment Success

Type[a]	Methotrexate (N=62)	Mycophenolate Mofetil (N=56)
	Number of Patients Reporting at Least One Event (%)	Number of Patients Reporting at Least One Event (%)
Non-Serious Ocular		
Visually significant cataract, surgery indicated	1 (1.6)	3 (5.4)
Suspect/confirmed glaucoma diagnosis	1 (1.6)	1 (1.8)
Ocular hypertension >24mm Hg	3 (4.8)	1 (1.8)
Other ocular event	16 (25.8)	16 (28.6)
Serious Ocular		
Ocular hypertension >24mm Hg	1 (1.6)	0 (0.0)
Non-Serious Laboratory		
SGOT or SGPT (2 to 5 times upper limit of normal <28 days)	7 (11.3)	0 (0.0)
Low hemoglobin (>6.5 to <9 g/dL lasting <28 days)	1 (1.6)	1 (1.8)
Serious Laboratory		
SGOT or SGPT (>5 times the upper limit of normal or 2 to 5 times upper limit of normal ≥28 days)[b]	2 (3.2)	0 (0.0)
Non-Serious Systemic		
Fatigue	26 (41.9)	21 (37.5)
Headache	20 (32.3)	13 (23.2)
Mood changes (self-reported, not requiring therapy)	13 (21.0)	9 (16.1)
Nausea	22 (35.5)	12 (21.4)
Muscle weakness, no decrease in function	13 (21.0)	6 (10.7)
Numbness or tingling	8 (12.9)	3 (5.4)
Diarrhea	5 (8.1)	9 (16.1)
Dyspnea	4 (6.5)	4 (7.1)
Vomiting	12 (19.4)	12 (21.4)
Allergic reaction	5 (8.1)	4 (7.1)
Fever <103 degrees for 12 hours	3 (4.8)	3 (5.4)
Systemic infection	11 (17.7)	7 (12.5)
Other systemic (no treatment required)	29 (46.8)	23 (41.1)
Serious Systemic		
Cancer	0 (0.0)	1 (1.8)
Muscle weakness, function limited or worse	1 (1.6)	0 (0.0)
Nausea	1 (1.6)	0 (0.0)

[a]Criteria for defining serious and non-serious adverse events included in eFigure 2

[b]All drug-related serious adverse events were due to elevated SGOT or SGPT (>5 times the upper limit of normal or 2 to 5 times the upper limit of normal for ≥28 days) and nausea

eTable 9. Six- to 12-Month Adverse Events from a RCT Comparing Methotrexate and Mycophenolate Mofetil for Noninfectious Uveitis in Patients Switching to the Other Antimetabolite

Type[a]	Methotrexate (N=29)	Mycophenolate Mofetil (N=20)
	Number of Patients Reporting at Least One Event (%)	Number of Patients Reporting at Least One Event (%)
Non-Serious Ocular		
Ocular hypertension >24mm Hg	2 (6.9)	3 (15.0)
Suspect/confirmed glaucoma diagnosis	1 (3.4)	0 (0.0)
Visually significant cataract, surgery indicated	4 (13.8)	4 (20.0)
Other ocular event	9 (31.0)	5 (25.0)
Serious Ocular		
Ocular hypertension, surgery required	1 (3.4)	0 (0.0)
Cataract surgery	1 (3.4)	0 (0.0)
Non-Serious Laboratory		
SGOT or SGPT(2 to 5 times upper limit of normal <28 days)	1 (3.4)	0 (0.0)
Low hemoglobin (>6.5 to <9 g/dL lasting <28 days)	0 (0.0)	1 (5.0)
Non-Serious Systemic		
Fatigue	13 (44.8)	13 (65.0)
Headache	12 (41.4)	8 (40.0)
Mood changes (self-reported, not requiring therapy)	9 (31.0)	7 (35.0)
Nausea	9 (31.0)	8 (40.0)
Muscle weakness, no decrease in function	8 (27.6)	2 (10.0)
Numbness or tingling	5 (17.2)	2 (10.0)
Diarrhea	6 (20.7)	4 (20.0)
Dyspnea	8 (27.6)	4 (20.0)
Vomiting	6 (20.7)	6 (30.0)
Allergic reaction	1 (3.4)	1 (5.0)
Fever <103 degrees for 12 hours	4 (13.8)	1 (5.0)
Systemic infection	11 (37.9)	6 (30.0)
Other systemic (no treatment required)	18 (62.1)	12 (60.0)
Serious Systemic		
Diarrhea[b]	0 (0.0)	1 (3.4)
Fatigue[b]	1 (3.4)	0 (0.0)

[a]Criteria for defining serious and non-serious adverse events included in eFigure 2
[b]All drug-related serious adverse events were due to diarrhea and fatigue