Title

Health- and Vision-Related Quality of Life in a Randomized Controlled Trial Comparing Methotrexate and Mycophenolate Mofetil for Uveitis

Journal

Ophthalmology, 128(9)

ISSN

0161-6420

Authors

Kelly, Nicole K
Chattopadhyay, Aheli
Rathinam, SR
et al.

Publication Date

2021-09-01

DOI

10.1016/j.ophtha.2021.02.024

Peer reviewed

HHS Public Access

Author manuscript

Ophthalmology. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Ophthalmology. 2021 September ; 128(9): 1337–1345. doi:10.1016/j.ophtha.2021.02.024.

Health and Vision-Related Quality of Life in a Randomized Controlled Trial Comparing Methotrexate and Mycophenolate Mofetil for Uveitis

Nicole K. Kelly, MPH[1], **Aheli Chattopadhyay**[1], **SR. Rathinam, MD, PhD**[2], **John A. Gonzales, MD**[1,3], **Radhika Thundikandy, MD**[2], **Anuradha Kanakath, MD**[4], **S. Bala Murugan, MD**[5], **R. Vedhanayaki, MD**[2], **Dean Cugley, MBBS**[6], **Lyndell L. Lim, MBBS, DMedSci**[6], **Eric B. Suhler, MD, MPH**[7], **Hassan A. Al-Dhibi, MD**[8], **Caleb D. Ebert, MPH**[1], **Elyse J. Berlinberg**[1], **Travis C. Porco, PhD, MPH**[1,3,9], **Nisha R. Acharya, MD, MS**[1,3,9] **FAST Research Group**

[1]F.I. Proctor Foundation, University of California, San Francisco, California

Corresponding Author: Nisha Acharya, MD, MS, F.I. Proctor Foundation, 490 Illinois St. 2nd Floor, University of California San Francisco, San Francisco, CA 94158 Tel: (415) 476-8131; Fax: (415) 476-0527. nisha.acharya@ucsf.edu.

Credit Roster for the FAST Research Group

Aravind Eye Hospital, Madurai, India: S.R. Rathinam, MD, PhD (Director); Radhika Thundikandy, MD; R. Vedhanayaki, MD; AL. Sivarama Subramanian; G. Jeyakohila; Gracy Evangelin; A.M. Azhagupandi; CV Praba; S. Bharati; Gomathi; N. J. Nirmaladevi; Mohammed Siddiq; B. Vijayakumar; S.R. Devi

Aravind Eye Hospital, Coimbatore, India: Anuradha Kanakath, MD (Director); V.R. Saravanan, MD; Upendra Babu, MD; R. Srija; S. Dhanalakshmi; R.R. Sakthimari; P.S. Keerthana; Mallika A.M.; C. Vasanthi; P.B. Mariselvi; P. Pandeeswari; S.M. Sudarvanitha; Prema

Aravind Eye Hospital, Pondicherry, India: S. Bala Murugan, MD (Director); Prabu Baskaran, MD; Madanagopalan, MD; Chokkahalli K. Nagesha, MD; R. Thilagavathi, Chitra; Krishnakumari; Irudhaya Raj P; S. Saravanan; Grace Mary, Nagarasi; Kiruba Gnansi

Asociación Para Evitar la Ceguera, Mexico City, Mexico: Lourdes Arellanes-Garcia, MD (Director); Luz Elena Concha del Rio, MD; Rashel Cheja Kalb, MD; Nancy Fernández, MD; Yoko Burgoa; Hilda Hernández; Roberto Fabela Cuello; Lorenzo Agustín Martínez Garcia; Ricardo Montoya Rodríguez; Maria del Carmen Preciado; Andrea Arreola

King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia: Hassan A. Al-Dhibi, MD (Director); Donald Stone, MD; Mohammed Al-Shamrani, MD; Sara Al-Nuwaysir; Abdulrahman Al-Hommadi; Abdullah Al-Omran; Saleh Al-Nasser; Gahram Al-Zahrani; Eman Mashan; Mizher Al-Ghamdi; Ayshah Al-Tuwejri

Northwestern University, Chicago, IL: Debra A. Goldstein, MD (Director); Anna Liza Castro-Malek; Gemma Dela Rosa; Marriner Skelly

Oregon Health and Science University, Portland, OR: Eric Suhler, MD, MPH (Director); James Rosenbaum, MD; Phoebe Lin, MD, PhD; Sherveen Salek, MD; Kristin Biggee, MD; Amde Shifera, MD, PhD; Laura Kopplin, MD, PhD; George Mount, MD; Tracy Giles; Susan Nolte; Ann Lundquist; Teresa Liesegang; Albert Romo; Chris Howell; Scott Pickell; Peter Steinkemp; Dawn Ryan; Jordan Barth, Jocelyn Hui, Chiedozie Ukachukwu

Royal Victorian Eye & Ear Hospital, East Melbourne, Australia: Lyndell Lim, MD (Director); Richard Stawell, MD; Robyn Troutbeck, MD; Cecilia Ling, MD; Xavier Fagan, MD; Julian Bosco, MD; Timothy Godfrey, MD; Tanya Pejnovic; Carly D'Sylva; Sutha Sanmugasundram; Tina-Marie van Tonder; Maria Kolic

University of California, San Francisco, CA: Nisha Acharya, MD, MS (Director); John Gonzales, MD; Thuy Doan, MD, PhD; Sarah Lopez, OD; Maya Rao, MPH; Erica Browne, MS; Betty Hom; Mary Lew, COT; Salena Lee, OD

Resource Centers

Coordinating Center, University of California, San Francisco, CA: Nisha Acharya, MD, MS; Travis Porco, PhD, MPH; Thomas Lietman, MD; Jeremy Keenan, MD, MPH; Eric Kim, MA; Hieu Nguyen, MS; Caleb Ebert, MPH; *Former members:* Maya Rao, MPH; Elyse Berlinberg, BS; Erica Browne, MS; Andrew Hirst, MS, Rachel Weinrib, MPH

Data and Safety Monitoring Committee: *Voting members*: Maureen G. Maguire, PhD (Chair); William E. Barlow, PhD; Steven Yeh, MD; Albert T. Vitale, MD; Jaqueline J. Glover, PhD; Narsing A. Rao, MD; *Former member.* Debra A. Goldstein, MD

National Eye Institute Program Director for Collaborative Clinical Research: Donald F. Everett, MA

Conflict of Interest: No conflicting relationship exists for any author.

This article contains additional online-only material. The following should appear online-only: Figure 3.

[2]Uvea Services, Aravind Eye Hospitals and Postgraduate Institute of Ophthalmology, Madurai, India

[3]Department of Ophthalmology, University of California, San Francisco, California

[4]Uvea Services, Aravind Eye Hospitals and Postgraduate Institute of Ophthalmology, Coimbatore, India

[5]Uvea Services, Aravind Eye Hospitals and Postgraduate Institute of Ophthalmology, Pondicherry, India

[6]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia

[7]Casey Eye Institute, Oregon Health and Science University, OHSU-PSU School of Public Health, and Portland Veterans' Affairs Health Care System, Portland, Oregon

[8]Division of Vitreoretinal Surgery and Uveitis, King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia

[9]Department of Epidemiology and Biostatistics, University of California, San Francisco, California

Abstract

Objective: To evaluate changes in health-related and vision-related quality of life (QoL) among patients with noninfectious uveitis who were treated with antimetabolites.

Design: Secondary analysis of a randomized controlled trial.

Participants: Patients with noninfectious uveitis from India, the United States, Australia, Saudi Arabia, and Mexico.

Methods: From 2013-2017, 216 participants were randomized to receive 25 mg weekly oral methotrexate or 1.5 g twice daily oral mycophenolate mofetil. Median changes in QoL were measured using Wilcoxon signed rank tests, and differences between treatment groups were measured using linear mixed models, adjusting for baseline QoL score, age, sex, and site. Among Indian patients, vision-related QoL scores from a general scale (NEI-VFQ) and a culturally specific scale (IND-VFQ) were compared using Pearson correlation tests.

Main Outcome Measures: Vision-related (NEI-VFQ and IND-VFQ) and health-related (PCS (physical component score) and MCS (mental component score) SF-36v2) QoL was measured at baseline, the primary endpoint (6 months or treatment failure before 6 months), and the secondary endpoint (12 months or treatment failure between 6-12 months).

Results: Among 193 participants who reached the primary endpoint, vision-related QoL increased from baseline by a median of 12.0 points (interquartile range (IQR)=1.0-26.1, NEI-VFQ scale), physical health-related QoL increased by a median of 3.6 points (IQR=−1.4-14.9, PCS SF-36v2), and mental health-related QoL increased by a median of 3.0 points (IQR=−3.7-11.9, MCS SF-36v2). These improvements in NEI-VFQ, SF-36v2 PCS, and SF-36v2 MCS scores were all significant ($p<0.01$). The linear mixed models showed that QoL did not differ between treatment groups for each QoL assessment (NEI-VFQ, IND-VFQ, PCS SF-36v2, and MCS SF-36v2; $p > 0.05$ for all). NEI-VFQ and IND-VFQ scores for Indian participants were highly

correlated at baseline and the primary and secondary endpoints (correlation coefficient=0.87, 0.80, 0.90, respectively).

Conclusions: Among patients treated with methotrexate or mycophenolate mofetil for uveitis, vision-related and health-related QoL significantly improved over the course of one year and did not differ by treatment allocation. These findings suggest that antimetabolites could improve overall patient well-being and daily functioning.

Precis:

Vision and health-related quality of life significantly increased among uveitis patients taking methotrexate or mycophenolate mofetil, regardless of antimetabolite. These improvements met or exceeded the minimal clinically important difference for each quality of life scale.

Introduction:

Uveitis, or inflammation within the eye, is a condition that may be chronic or recurrent in nature and can significantly impact a person's mental and physical well-being.[1–4] This inflammation contributes to global ocular morbidity as uveitis can cause visual impairment and blindness. Unlike other eye conditions that primarily affect older adults, such as cataracts, glaucoma, and macular degeneration, uveitis disproportionately affects people of working age[5] and results in a greater loss of workplace productivity.[6,7] Furthermore, non-infectious uveitis often requires long-term immunosuppressive treatment that may cause adverse systemic effects that impair mental and physical health.[8,9]

Many studies have evaluated the effectiveness of interventions to treat uveitis by measuring outcomes such as visual acuity or control of inflammation.[10–12] However, these clinical measures are limited in scope and may not reflect the complete patient experience captured by other physical and mental health outcomes.[8,13] In contrast, quality of life (QoL) is a well-documented health indicator that provides a more comprehensive understanding of patient outcomes compared to traditional ocular measures. Various instruments have been developed and validated to measure health-related quality of life (HR-QoL)[14] and vision-related quality of life (VR-QoL),[15] and some ophthalmology trials now report these measures as secondary treatment outcomes.[16–18] In particular, QoL is a crucial measure to report for uveitis trials since patients with uveitis tend to have a lower QoL compared to the general population or to patients with other eye diseases.[1–3]

However, limited information exists on QoL among uveitis patients taking specific immunosuppressive therapies. Treatment is often long-term and may have implications for both physical and mental well-being. Previous studies have focused on QoL among uveitis patients using other therapies, such as fluocinolone acetonide implants or systemic corticosteroids combined with various immunosuppressive therapies.[2,17,19] One small clinical trial compared antimetabolite use for noninfectious uveitis and found that despite improvements in VR-QoL, 6 months of immunosuppressive treatment minimally impacted physical health and negatively affected mental health.[16] However, the findings from this study were limited in power and generalizability. Furthermore, most QoL scales have been validated and standardized for use in high-income settings,[14,15,20] yet uveitis accounts for

a substantially higher proportion of blindness in low-and-middle income countries.[5,21–24] Localized versions of VR-QoL instruments have been developed for use in countries such as India[25]; however, it remains unclear whether general and culturally-specific VR-QoL scales provide comparable measures in an Indian setting.

In the First-line Antimetabolites as Steroid-sparing Treatment (FAST) Trial,[10] uveitis patients were randomized to receive one of two corticosteroid-sparing treatments, either methotrexate or mycophenolate mofetil. To better understand the comprehensive effects of immunosuppressive agents on uveitis patients, this secondary analysis aims to 1) report changes in VR-QoL and HR-QoL from the trial, 2) measure the association between type of antimetabolite treatment and QoL, and 3) evaluate whether general VR-QoL scores and culturally-specific VR-QoL scores were comparable among a subset of Indian patients.

Methods:

Study design

The FAST Trial (ClinicalTrials.gov: NCT01829295)[10] was a randomized, observer-masked clinical trial that compared the effectiveness of two common corticosteroid-sparing antimetabolite treatments, methotrexate and mycophenolate mofetil, among patients with noninfectious intermediate, posterior, and pan-uveitis. From August 2013 - August 2017, we prospectively enrolled participants at nine centers throughout India, the United States, Australia, Saudi Arabia, and Mexico. Participants were block randomized in a 1:1 ratio using random permutations of sizes 4 and 6 (stratified by study site) to receive either oral methotrexate (25 mg weekly) or oral mycophenolate mofetil (1.5 g twice daily). Patients were also treated with a standardized oral prednisone taper following Standardization of Uveitis Nomenclature guidelines.[26] All participants were at least sixteen years of age, had active noninfectious intermediate, posterior, or pan-uveitis in at least one eye, and had an indication for starting corticosteroid-sparing therapy. Investigators obtained ethical approval from local institutional review boards, all participants provided written informed consent, and all research procedures adhered to the tenets of the Declaration of Helsinki. Additional details about the trial and primary results have been published.[10]

Study timeline & treatment outcome

Participants were followed prospectively for up to 12 months. This secondary analysis examines QoL outcomes at baseline, the primary study endpoint, and the secondary study endpoint. The primary endpoint was defined as 6 months since enrollment, or the time of treatment failure prior to 6 months. Participants were considered to have achieved treatment success if both eyes had: 1) ≤0.5+ anterior chamber cells, ≤0.5+ vitreous haze, and no active retinal or choroidal lesions, 2) 7.5 mg of prednisone and ≤2 drops of prednisolone acetate 1% a day, and 3) no declaration of treatment failure because of intolerability or safety. Treatment failure due to efficacy was declared if condition 1 or 2 was not met by 6 months; treatment failure due to safety or intolerability could be declared at any time. Following the primary endpoint, participants either continued on their initial treatment, in the case of treatment success, or switched to the alternate antimetabolite, in the case treatment failure. Participants could exit the trial prior to the secondary endpoint (defined

as 12 months since enrollment, or the time of treatment failure between 6-12 months) if a serious laboratory safety event occurred or if the decision was made to pursue alternative treatment. For the purpose of this analysis, participants who experienced treatment failure at the primary endpoint and subsequently switched treatments were excluded from analyses at the secondary study endpoint.

Quality of life outcomes

The primary outcomes in this analysis were VR- and HR-QoL measured at the primary study endpoint. All participants completed the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ),[15] an instrument measuring VR-QoL, and the Medical Outcomes Study 36-Item Short Form Survey (SF-36v2),[14] an instrument measuring HR-QoL, at enrollment, the primary study endpoint, and the secondary study endpoint. The NEI-VFQ and the SF-36v2 are two commonly used questionnaires in ophthalmology trials, and the NEI-VFQ has been translated and adapted for various languages and cultural contexts, including a Tamil version validated for use in southern India (Indian Visual Functioning Questionnaire, IND-VFQ).[25,27] In addition to the NEI-VFQ and SF-36v2, participants enrolled in India also completed the IND-VFQ. A coordinator who was unmasked to each participant's treatment assignment administered the questionnaires; masked physicians were not present when the questionnaires were administered.

Vision-related quality of life

NEI-VFQ-25—The NEI-VFQ-25 (NEI-VFQ) is a validated VR-QoL questionnaire that measures functioning and well-being in physical, mental, and social aspects of a patient's life and is specifically designed for use in vision studies.[15] The NEI-VFQ contains 25 questions graded on a Likert-type scale for rating the degree of severity of visual symptoms or difficulty of vision-related tasks (e.g., driving, reading a newspaper). Responses can be used to calculate a general health subscale as well as 12 VR-QoL subscales. An overall composite score on a scale of 0 (worst) to 100 (best) was calculated as the unweighted average of sub-scores for the twelve categories. The NEI-VFQ was not developed specifically for uveitis patients but has been frequently used for this group, and 4-6 points is considered a clinically meaningful difference on the scale.[17,18,28,29]

IND-VFQ—The IND-VFQ is a validated adaptation of the NEI-VFQ that was developed to be applicable for an Indian population.[27] The IND-VFQ consists of 33 questions and three subscales: a general functioning scale, psychosocial impact scale, and visual symptoms scale.[25] Like the NEI-VFQ, all questions are graded on a Likert-type scale rating the severity of symptoms or degree of difficulty completing a task. However, findings from a recent Rasch analysis demonstrated a higher validity of the IND-VFQ when using four sub-scales instead of three (vision-specific mobility, activity limitation, psychosocial impact, and visual symptoms).[30] Therefore, an overall composite IND-VFQ score was calculated as the mean of the scores from each of the four functional categories.[30] A Tamil version of the scale has been extensively tested and validated for use in south Indian patients with uveitis.[31]

Health-related quality of life

SF-36v2—The SF-36v2 evaluates HR-QoL by assessing a patient's self-perception of their physical and mental health.[14] It contains 36 questions graded on a 5-point Likert scale except for one question, which uses a 3-point Likert scale. The questionnaire can be divided into two components, physical and mental health, and eight domains: physical functioning, role limitations caused by physical health, bodily pain, general health perceptions, vitality (energy and fatigue), general mental health (psychological distress), role limitations because of emotional problems, and social functioning limitations because of emotional problems. Scores are normalized to a United States population and are reported on a scale from 0-100, where 0 corresponds to the most severe disability. All SF-36v2 scores were calculated using QualityMetrics.[32] In this analysis, we present the physical component score (PCS) and mental component score (MCS) as separate measures; 3-5 points is considered a clinically meaningful difference for the composite SF-36v2 score, with a similar range used when interpreting PCS and MCS changes.[33–35]

Statistical analysis

To address the first aim of this analysis, we determined the median QoL scores and interquartile ranges (IQRs) for each of the four scales (NEI-VFQ, IND-VFQ, SF-36v2 PCS, and SF-36v2 MCS) at baseline, the primary outcome, and the secondary outcome. Changes in QoL were evaluated by using Wilcoxon signed rank tests to compare baseline QoL scores to those at the primary and secondary study endpoints. We employed non-parametric testing because the distribution of QoL scores was non-normal. For the second aim, linear mixed models were used to compare QoL scores at the primary outcome by treatment group and by treatment outcome. All multivariable models controlled for baseline QoL score, age, sex, and site (included as a random effect), as was pre-specified in the FAST statistical analysis plan.[12] For each linear mixed model, the average adjusted change in QoL score was reported as beta (β). For the third aim, we compared NEI-VFQ and IND-VFQ scores among participants enrolled in India using Pearson correlation tests. All statistical tests were two-sided using an alpha of 0.05; all statistical analyses were performed using R version 3.6.1 (R Project for Statistical Computing).

Results:

Participant inclusion & baseline demographics

Two hundred sixteen participants were randomized and enrolled from August 22, 2013 to August 16, 2017. Of the 216 participants, 193 (89.4%) reached the primary endpoint with complete QoL information and were subsequently included in this analysis (Figure 1). Baseline demographic and clinical characteristics are presented in Table 1 and were balanced between treatment groups, with the exception of sex. A higher proportion of participants randomized to methotrexate were female (72.9%) compared to those randomized to mycophenolate mofetil (60.8%). In general, the majority of FAST participants were female (66.8%), enrolled in India (61.7%), and had a diagnosis of posterior or pan-uveitis (79.3%). Additional participant demographic and clinical characteristics can be found in the primary paper.[10]

Vision-Related Quality of Life

Improvements in VR-QoL throughout the trial—VR-QoL significantly improved among participants over the course of the trial (Table 2, Figure 2). The median NEI-VFQ score improved from 61.9 (interquartile range (IQR): 48.2-80.3) at baseline to 81.5 (IQR: 68.6-93.4) by the primary endpoint (Wilcoxon signed rank test: $p<0.001$); the median change in NEI-VFQ during this period was 12.0 points (IQR: 1.0-26.1). Among participants enrolled in India, the median IND-VFQ score significantly increased from 69.6 (IQR: 42.0-80.2) at baseline to 91.1 (IQR: 76.2-100.0) by the primary endpoint ($p<0.001$) with a median change of 16.9 points (IQR: 3.9-41.6). Statistically significant improvements were observed between baseline and the secondary endpoint on the NEI-VFQ and IND-VFQ (NEI-VFQ median score changed from 61.9 (IQR: 48.2-80.3) to 84.0 (IQR: 70.2-95.9); IND-VFQ median score changed from 69.6 (IQR: 42.0-80.2) to 92.8 (IQR: 76.9-100.0); $p<0.001$ for both); however, improvements from the primary to secondary endpoint were only statistically significant on the IND-VFQ scale (NEI-VFQ median score changed from 81.5 (IQR: 68.6-93.4) to 84.0 (IQR: 70.2-95.9) ($p=0.07$); IND-VFQ changed from 91.1 (IQR: 76.2-100.0) to 92.8 (IQR: 76.9-100.0) ($p=0.02$)) (Table 2).

Differences in VR-QoL by treatment group & treatment outcome—Participants randomized to methotrexate experienced a median improvement of 14.8 points (IQR: 1.5-33.8) on the NEI-VFQ scale and 17.5 points (IQR: 5.0-43.9) on the IND-VFQ scale; those randomized to mycophenolate mofetil experienced a median improvement of 8.5 points (IQR: 0.2-24.0; NEI-VFQ scale) and 16.7 points (IQR: 1.4-29.2; IND-VFQ scale). Statistically significant differences in VR-QoL were not observed between treatment groups: in a linear mixed model, the adjusted average difference (β) in VR-QoL at the primary endpoint among participants taking methotrexate compared to mycophenolate mofetil was 2.2 points (95% confidence interval (CI)= −1.4-5.8, $p=0.23$; NEI-VFQ). Among participants enrolled in India, the average difference between treatment groups at the primary endpoint was 3.9 points (95% CI= −1.5-9.3, $p=0.16$; IND-VFQ) (Table 3). However, VR-QoL differed significantly between participants who achieved treatment success compared to those who did not (NEI-VFQ: β= 9.8, 95% CI=6.2-13.5, $p<0.001$; IND-VFQ: β=15.4, 95% CI=10.2-20.8, $p<0.001$).

Health-related Quality of life

Improvements in HR-QoL throughout the trial—Both physical and mental HR-QoL improved throughout the trial (Table 2, Figure 2). Participants' median SF36-v2 PCS score increased from 44.1 (IQR: 39.4-52.1) at baseline to 52.2 (IQR: 44.8-57.2) by the primary endpoint ($p<0.001$) where the median change was 3.6 points (IQR: −1.4-14.9). The median SF36-v2 MCS score increased from 41.0 (IQR: 36.6-48.8) to 47.1 (IQR: 38.3-53.1) ($p=0.002$) during this period with a median change of 3.0 points (IQR: −3.7-11.9). Similar to trends observed for VR-QoL, PCS and MCS significantly improved from baseline to the secondary endpoint (PCS median score changed from 44.1 (IQR: 39.4-52.1) to 52.4 (IQR: 45.1-57.1) ($p<0.001$); MCS median score changed from 41.0 (IQR: 36.6-48.8) to 46.4 (39.9-57.0) ($p=0.002$); however, a significant increase was not observed from the primary to secondary endpoint (PCS median score changed from 52.2 (IQR: 44.8-57.2) to 52.4 (IQR:

45.1-57.1) (p=0.11); MCS median score changed from 47.1 (IQR: 38.3-53.1) to 46.4 (IQR: 39.9-57.0) (p=0.99)) (Table 2).

Differences in HR-QoL by treatment group & treatment outcome—Participants randomized to methotrexate experienced a median change of 3.6 points (IQR: −0.9-16.2) on the PCS and 4.0 points (IQR: −4.0-13.9) on the MCS; the median change among participants randomized to mycophenolate mofetil was 3.5 points (IQR: −1.8-13.8; PCS) and 2.5 points (IQR: −3.7-10.3; MCS). Statistical models revealed that physical and mental HR-QoL was comparable between treatment groups at the primary endpoint (PCS: β= 0.6, 95% CI= −1.3-2.6, p=0.51; MCS: β=−0.5, 95% CI=−3.2-2.2, p=0.72) (Table 3); however, HR-QoL was significantly higher among participants who achieved treatment success compared to those who did not (PCS: β=3.6, 95%CI=1.6-5.5, p<0.001; MCS: β=3.7, 95%CI=1.0-6.5, p<0.001).

General versus culturally-specific QoL measures

NEI-VFQ and IND-VFQ scores were highly correlated among participants enrolled in India at baseline, the primary endpoint, and the secondary endpoint (Pearson correlation coefficient (r)=0.88, 0.84, 0.90, respectively) (Figure 3 (available at http://www.aaojournal.org)). The change in NEI-VFQ and IND-VFQ from baseline to the primary endpoint was highly correlated (r=1.00).

Discussion

Clinically meaningful improvements in VR and HR-QoL were observed in patients treated with either methotrexate or mycophenolate mofetil. These findings are consistent with the trial's primary outcome which found that corticosteroid-sparing control of inflammation did not differ by use of methotrexate or mycophenolate mofetil.[10] This secondary analysis also demonstrates how antimetabolites, along with a corticosteroid taper, can significantly improve the overall physical and mental well-being of patients with noninfectious uveitis. Improvements in QoL were observed regardless of whether or not participants achieved control of their ocular inflammation; however, the magnitude of these gains varied by treatment outcome. On all four QoL scales, participants who did not achieve corticosteroid-sparing control of ocular inflammation had substantially lower VR and HR-QoL, indicating that inflammation likely impaired visual functioning, and in turn, physical and mental well-being. Of note, treatment failures were mostly due to lack of efficacy (81% of failures in the methotrexate group and 90% in the mycophenolate mofetil group), rather than intolerability or safety.

Improvements in QoL were observed at the primary outcome but did not significantly increase between 6 and 12 months. This trend suggests that most improvements in QoL occur in the first 6 months after treatment initiation but are sustained for at least one year. Due to the chronic nature of uveitis, patients may be treated for extended periods of time; thus, it is essential to fully understand any long-term physical and/or mental health implications associated with antimetabolite use. Given the study's timeline, it remains unclear whether increased QoL may be maintained beyond one year. However, these results provide evidence of rapid and clinically meaningful improvements in physical and mental

health. Such improvements could have the potential to offset some of the loss in workplace productivity and reduced daily functioning that is associated with uveitis.[6,7] Currently, there is limited evidence[16] as to whether or not effective treatment could mitigate this burden through significant gains in QoL. While this analysis did not explicitly include markers of workplace productivity (e.g., quality-adjusted life years or disability-adjusted life years), it provides rigorous evidence of comprehensive physical and mental health improvements, including the ability to conduct daily activities (measured as physical functioning and role limitations on the PCS SF-36v2). Thus, we hypothesize that methotrexate and mycophenolate mofetil could possibly reduce the burden of disease and increase workplace productivity among uveitis patients, most of whom are of working age.[5] Future studies could assess the cost-effectiveness of antimetabolite use among uveitis patients to better understand effects on productivity and examine longitudinal trends in QoL.

This study found that antimetabolite use over the course of one year considerably improved the physical and mental health of patients to a clinically meaningful degree. Beyond statistical significance, increases in VR-QoL and HR-QoL met or exceeded the minimal clinically important difference (MCID) definition on each scale (defined as: NEI-VFQ MCID: 4-6 points,[28] IND-VFQ MCID: ≥0.5 times the standard deviation of the mean[36] (11.8 points), and SF-36v2 MCID: 3-5 points[33]). Larger improvements were observed for VR-QoL than HR-QoL. Median changes in the PCS and MCS SF-36v2 from baseline to the primary endpoint met the threshold for clinically meaningful improvement. Additionally, median changes in the NEI-VFQ score were 2-3 times the MCID and changes in the IND-VFQ score were 1.4 times the MCID.

Since uveitis primarily affects vision, it is logical that treatment intended to control ocular inflammation would improve VR-QoL more than general HR-QoL. However, methotrexate and mycophenolate mofetil are systemic treatments that can be associated with side effects. Even though few serious adverse events occurred during the FAST Trial, non-serious systemic adverse events such as fatigue and nausea were relatively common and could have impacted HR-QoL.[10] SF-36v2 has been demonstrated to robustly capture the treatment experience with medication side effects, reflected by lower scores indicating a decrease in quality of life.[37,38] Thus, HR-QoL is an important outcome measure because it provides a comprehensive understanding of the patient experience, especially for chronic conditions such as uveitis that can adversely affect physical and mental health.[1–3]

This analysis employed validated scales (SF-36v2, NEI-VFQ, and IND-VFQ) to measure QoL and provide a comprehensive measure of health and well-being instead of relying solely on ocular outcomes. A recent study found that common ocular measures fail to appropriately capture outcomes deemed most important by uveitis patients, and that reporting HR-QoL helps bridge this gap.[8] However, a uveitis-specific QoL instrument does not currently exist for adult patients, so our understanding of patients' well-being may still be incomplete.

The choice of QoL scales in this analysis was driven by the availability of instruments and by the intent to measure: 1) general HR-QoL that would be comparable across clinical settings (SF-36v2); 2) VR-QoL (NEI-VFQ) given the impact of uveitis on vision; and 3)

VR-QoL in an Indian cultural context (IND-VFQ). The results from this analysis suggest that NEI-VFQ and IND-VFQ scores were comparable among participants enrolled in India given that: 1) NEI-VFQ and IND-VFQ scores were highly correlated at all time points, 2) significant QoL improvements were observed on both scales, and 3) QoL improvements did not differ by treatment allocation on either scale.

This study was the first of its kind to evaluate QoL among uveitis patients taking antimetabolites across different cultural settings using a sufficiently powered, randomized design. The rigorous design and high level of generalizability contribute to the evidence base that antimetabolites can significantly improve VR and HR-QoL among uveitis patients. However, this study contains several limitations. First, the trial lacked a comparison group of participants who were not currently receiving treatment for their uveitis. Although we observed statistically significant gains in QoL, there may have been underlying secular trends that were responsible for the improvements in both groups. This is evident with placebo trials where patients report an improvement in their quality of life regardless of receiving active drug or placebo.[39] A placebo group would have more clearly indicated the effect of antimetabolite treatment; however, this may have violated equipoise since it is standard of care to treat uveitis. In addition, the magnitude of the change in quality of life measured may have been greater because we provided study medications at no cost to all participants. There may have been underlying confounding variables that masked the true association between QoL and antimetabolite treatment and/or treatment outcome. Since antimetabolite treatment was randomly allocated and baseline covariates were balanced across treatment groups, there was likely little confounding in the analysis that compared QoL by treatment group. In addition, it is possible that the patients lost to follow-up may have been doing more poorly than the patients who remained in the trial. However, the loss to follow-up was low at 10% and was equal between treatment groups. We had accounted for a 10% loss to follow-up in the trial design. Additionally, in our primary analysis, we conducted a sensitivity analysis on these missing patients using multiple imputation as pre-specified in our statistical analysis plan, and it did not change the primary outcome results. We do not believe that the small number of patients who were lost to follow-up would be likely to significantly change the outcome. Lastly, the QoL scales in this analysis were not specifically designed for uveitis patients and may not accurately or fully reflect patients' experiences. A paucity of disease-specific QoL measures calls for future efforts to develop and validate such scales.[8]

This study found that the antimetabolites methotrexate and mycophenolate mofetil significantly improved the physical and mental well-being of patients with noninfectious uveitis over the course of one year, with comparable improvement with each medication. Increases in HR and VR-QoL met or exceeded the MCID which suggests that these improvements translated to meaningful health benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: This study received support from NEI cooperative agreement U10 EY021125. The Department of Ophthalmology at UCSF is supported by an unrestricted grant from the Research to Prevent Blindness Foundation, a core grant (EY06190) from the NEI, and That Man May See Foundation. The sponsors had no role in the design or conduct of this research.

Abbreviations and Acronyms:

QoL	quality of life
VR-QoL	vision related quality of life
HR-QoL	health related quality of life
FAST	First-line Antimetabolites as Corticosteroid Sparing Treatment
NEI-VFQ	National Eye Institute Visual Functioning Questionnaire
SF-36v2	Medical Outcomes Study 36-Item Short Form Survey
IND-VFQ	Indian Visual Functioning Questionnaire
PCS	physical component score
MCS	mental component score
IQR	interquartile range
β	average change
95% CI	95% confidence interval
r	Pearson correlation coefficient
MCID	minimal clinically important difference

References

1. Hui MM, Wakefield D, Patel I, Cvejic E, McCluskey PJ, Chang JH. Visual Functioning and Health-related Quality-of-Life are Compromised in Patients with Uveitis. Ocul Immunol Inflamm. 2017;25(4):486–491. doi:10.3109/09273948.2016.1139734 [PubMed: 27002552]
2. Miserocchi E, Modorati G, Mosconi P, Colucci A, Bandello F. Quality of Life in Patients with Uveitis on Chronic Systemic Immunosuppressive Treatment. Ocul Immunol Inflamm. 2010;18(4):297–304. doi:10.3109/09273941003637510 [PubMed: 20482406]
3. Qian Y, Glaser T, Esterberg E, Acharya NR. Depression and Visual Functioning in Patients with Ocular Inflammatory Disease. Am J Ophthalmol. 2012;153(2):370–378.e2. doi:10.1016/j.ajo.2011.06.028 [PubMed: 21924399]
4. de Smet MD, Taylor SRJ, Bodaghi B, et al.Understanding uveitis: The impact of research on visual outcomes. Prog Retin Eye Res. 2011 ;30(6):452–470. doi:10.1016/j.preteyeres.2011.06.005 [PubMed: 21807112]
5. Tsirouki T, Dastiridou A, Symeonidis C, et al.A Focus on the Epidemiology of Uveitis. Ocul Immunol Inflamm. 2018;26(1):2–16. doi:10.1080/09273948.2016.1196713 [PubMed: 27467180]
6. Harrabi H, Aubin M-J, Zunzunegui MV, Haddad S, Freeman EE. Visual difficulty and employment status in the world. PloS One. 2014;9(2):e88306. doi:10.1371/journal.pone.0088306 [PubMed: 24516632]

7. Hong T, Mitchell P, Burlutsky G, Fong CS-U, Rochtchina E, Wang JJ. Visual impairment and subsequent use of support services among older people: longitudinal findings from the Blue Mountains Eye Study. Am J Ophthalmol. 2013;156(2):393–399.e1. doi:10.1016/j.ajo.2013.04.002 [PubMed: 23688709]
8. Stolk-Vos AC, Kasigar H, Nijmeijer KJ, et al.Outcomes in patients with chronic uveitis: which factors matter to patients? A qualitative study. BMC Ophthalmol. 2020;20. doi:10.1186/s12886-020-01388-y [PubMed: 31918696]
9. Tallouzi MO, Moore DJ, Bucknall N, et al.Outcomes important to patients with non-infectious posterior segment-involving uveitis: a qualitative study. BMJ Open Ophthalmol. 2020;5(1):e000481. doi:10.1136/bmjophth-2020-000481
10. Rathinam SR, Gonzales JA, Thundikandy R, et al.Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial. JAMA. 2019;322(10):936–945. doi:10.1001/jama.2019.12618 [PubMed: 31503307]
11. Kempen JH, Altaweel MM, Holbrook JT, et al.Randomized Comparison of Systemic Anti-inflammatory Therapy Versus Fluocinolone Acetonide Implant for Intermediate, Posterior and Panuveitis: The Multicenter Uveitis Steroid Treatment Trial. Ophthalmology. 2011;118(10):1916–1926. doi:10.1016/j.ophtha.2011.07.027 [PubMed: 21840602]
12. Denniston AK, Holland GN, Kidess A, et al.Heterogeneity of primary outcome measures used in clinical trials of treatments for intermediate, posterior, and panuveitis. Orphanet J Rare Dis. 2015;10. doi:10.1186/s13023-015-0318-6 [PubMed: 25648394]
13. Dean S, Mathers JM, Calvert M, et al.“The patient is speaking”: discovering the patient voice in ophthalmology. Br J Ophthalmol. 2017;101(6):700–708. doi:10.1136/bjophthalmol-2016-309955 [PubMed: 28455280]
14. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I.Conceptual framework and item selection. Med Care. 1992;30(6):473–483. [PubMed: 1593914]
15. Mangione CM, Lee PP, Gutierrez PR, et al.Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol Chic Ill 1960. 2001;119(7):1050–1058. doi:10.1001/archopht.119.7.1050
16. Niemeyer KM, Gonzales JA, Rathinam SR, et al.Quality of Life Outcomes from a Randomized Clinical Trial Comparing Antimetabolites for Intermediate, Posterior, and Panuveitis. Am J Ophthalmol. 2017;179:10–17. doi:10.1016/j.ajo.2017.04.003 [PubMed: 28414043]
17. Sugar EA, Venugopal V, Thorne JE, et al.Longitudinal Vision-Related Quality of Life for Patients with Noninfectious Uveitis Treated with Fluocinolone Acetonide Implant or Systemic Corticosteroid Therapy. Ophthalmology. 2017;124(11):1662–1669. doi:10.1016/j.ophtha.2017.05.015 [PubMed: 28624167]
18. Sheppard J, Joshi A, Betts KA, et al.Effect of Adalimumab on Visual Functioning in Patients With Noninfectious Intermediate Uveitis, Posterior Uveitis, and Panuveitis in the VISUAL-1 and VISUAL-2 Trials. JAMA Ophthalmol. 2017;135(6):511–518. doi:10.1001/jamaophthalmol.2017.0603 [PubMed: 28426849]
19. Frick KD, Drye LT, Kempen JH, et al.Associations among visual acuity and vision- and health-related quality of life among patients in the multicenter uveitis steroid treatment trial. Invest Ophthalmol Vis Sci. 2012;53(3):1169–1176. doi:10.1167/iovs.11-8259 [PubMed: 22247489]
20. Herdman M, Gudex C, Lloyd A, et al.Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 ;20(10):1727–1736. doi:10.1007/s11136-011-9903-x [PubMed: 21479777]
21. Acharya NR, Tham VM, Esterberg E, et al.Incidence and Prevalence of Uveitis: Results From the Pacific Ocular Inflammation Study. JAMA Ophthalmol. 2013;131(11):1405–1412. doi:10.1001/jamaophthalmol.2013.4237 [PubMed: 24008391]
22. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. Br J Ophthalmol. 1996;80(9):844–848. [PubMed: 8962842]
23. Rathinam SR, Namperumalsamy P. Global variation and pattern changes in epidemiology of uveitis. Indian J Ophthalmol. 2007;55(3):173–183. doi:10.4103/0301-4738.31936 [PubMed: 17456933]

24. London NJS, Rathinam SR, Cunningham ET. The Epidemiology of Uveitis in Developing Countries. Int Ophthalmol Clin. 2010;50(2):1–17. doi:10.1097/IIO.0b013e3181d2cc6b
25. Gupta SK, Viswanath K, Thulasiraj RD, et al.The development of the Indian vision function questionnaire: field testing and psychometric evaluation. Br J Ophthalmol. 2005;89(5):621–627. doi:10.1136/bjo.2004.050732 [PubMed: 15834097]
26. Jabs DA, Rosenbaum JT, Foster CS, et al.Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000;130(4):492–513. doi:10.1016/s0002-9394(00)00659-0 [PubMed: 11024423]
27. Murthy GVS, Gupta SK, Thulasiraj RD, Viswanath K, Donoghue EM, Fletcher AE. The development of the Indian vision function questionnaire: questionnaire content. Br J Ophthalmol. 2005;89(4):498–503. doi:10.1136/bjo.2004.047217 [PubMed: 15774932]
28. Suñer IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. Invest Ophthalmol Vis Sci. 2009;50(8):3629–3635. doi:10.1167/iovs.08-3225 [PubMed: 19255158]
29. Sugar EA, Burke AE, Venugopal V, Thorne JE, Holbrook JT. Responsiveness of Vision-Specific and General Quality of Life Metrics to Ocular and Systemic Events in Patients with Uveitis. Ophthalmology. 2020;127(12):1710–1718. doi:10.1016/j.ophtha.2020.07.038 [PubMed: 32717341]
30. Finger RP, Kupitz DG, Holz FG, et al.The impact of the severity of vision loss on vision-related quality of life in India: an evaluation of the IND-VFQ-33. Invest Ophthalmol Vis Sci. 2011 ;52(9):6081–6088. doi:10.1167/iovs.11-7388 [PubMed: 21693607]
31. Venkataraman A, Rathinam S. A pre- and post-treatment evaluation of vision-related quality of life in uveitis. Indian J Ophthalmol. 2008;56(4):307–312. [PubMed: 18579990]
32. Maruish ME, Turner-Bowker DM. A Guide to the Development of Certified Modes of Short Form Survey Administration. Published online Lincoln, RI: QualityMetric Inc2009.
33. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes. 2003;1:4. doi:10.1186/1477-7525-1-4 [PubMed: 12737635]
34. MCHORNEY CA, JOHNE WJR, ANASTASIAE R. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and Clinical Tests of Validity in Measuring Physical and Mental Health Constructs. Med Care. 1993;31(3). https://journals.lww.com/lww-medicalcare/Fulltext/1993/03000/The_MOS_36_Item_Short_Form_Health_Survey_SF_36_.6.aspx
35. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JEJ. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum. 2000;43(7):1478–1487. doi:10.1002/1529-0131(200007)43:7<1478::AID-ANR10>3.0.CO;2-M [PubMed: 10902749]
36. Finger RP, Kupitz DG, Fenwick E, et al.The Impact of Successful Cataract Surgery on Quality of Life, Household Income and Social Status in South India. PLoS ONE. 2012;7(8). doi:10.1371/journal.pone.0044268
37. Ruta DA, Hurst NP, Kind P, Hunter M, Stubbings A. Measuring health status in British patients with rheumatoid arthritis: reliability, validity and responsiveness of the short form 36-item health survey (SF-36). Br J Rheumatol. 1998;37(4):425–436. doi:10.1093/rheumatology/37.4.425 [PubMed: 9619895]
38. Gentile S, Beauger D, Speyer E, et al.Factors associated with health-related quality of life in renal transplant recipients: results of a national survey in France. Health Qual Life Outcomes. 2013;11:88. doi:10.1186/1477-7525-11-88 [PubMed: 23721430]
39. Gupta AK, Langley RG, Lynde C, et al.ISA247: Quality of Life Results from a Phase II, Randomized, Placebo-Controlled Study. J Cutan Med Surg. 2008;12(6):268–275. doi:10.2310/7750.2008.07060 [PubMed: 19317948]

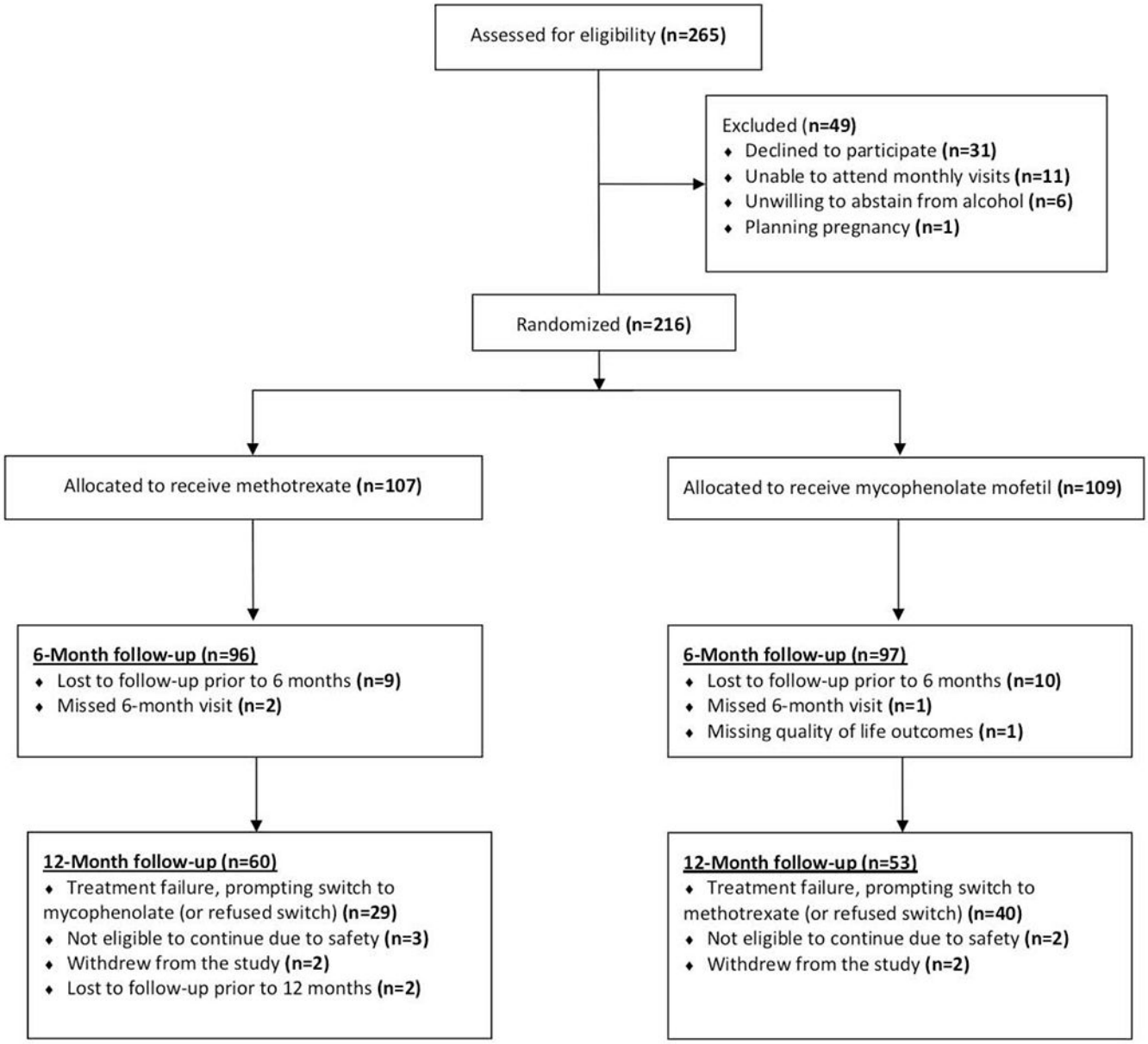

Figure 1.

Flow of participants in the FAST Trial who were randomized to receive either methotrexate or mycophenolate mofetil for noninfectious uveitis

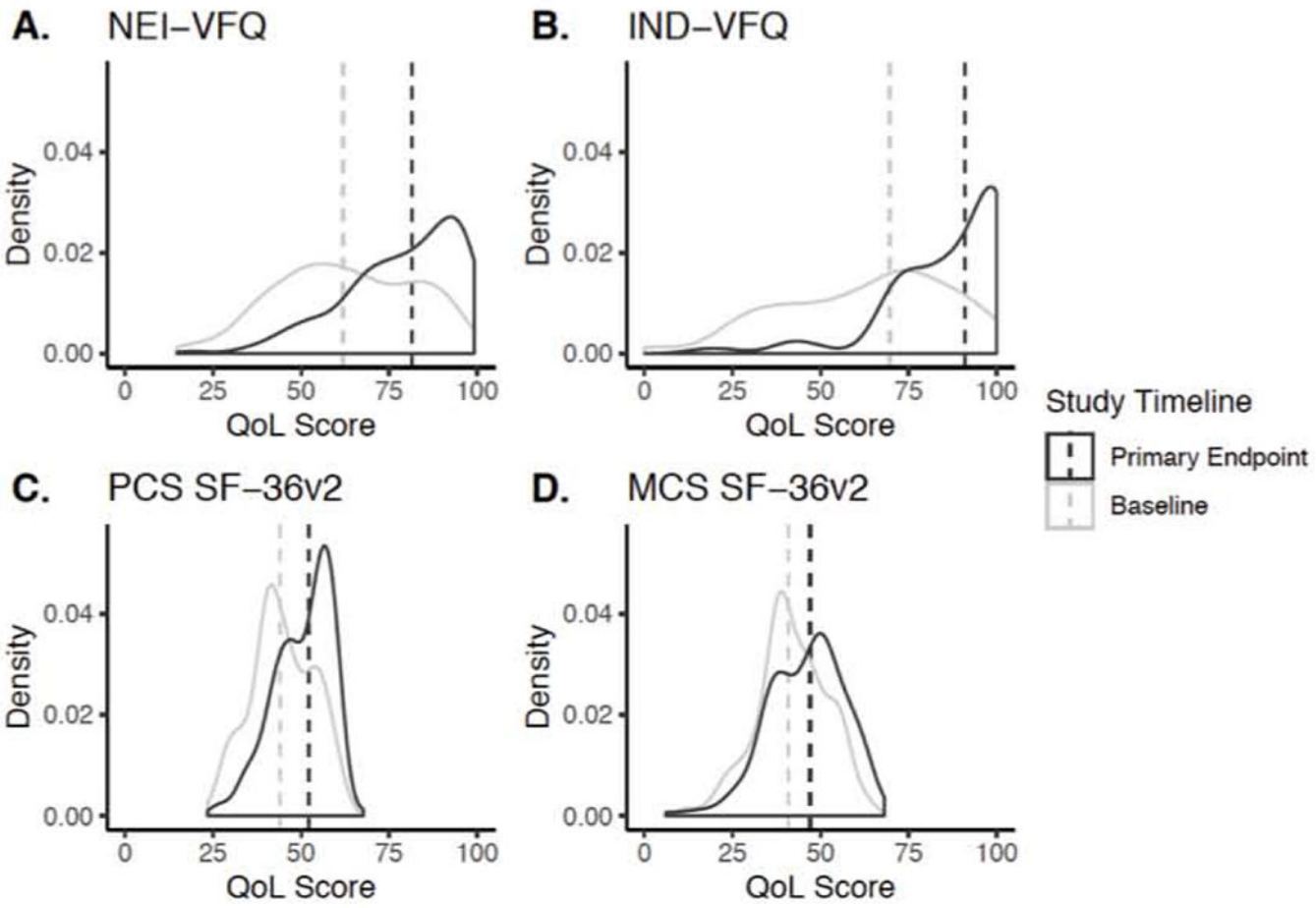

Figure 2.

Distribution of vision and health-related quality of life scores at baseline and the primary study endpoint for all participants[a,b,c]

[a]Quality of life scales, clockwise from top left: National Eye Institute Visual Functioning Questionnaire (NEI-VFQ); Indian Vision Function Questionnaire (IND-VFQ; Indian participants only); mental component score of the Medical Outcomes Study 36-Item Short Form Survey (MCS SF-36v2); physical component score of the Medical Outcomes Study 36-Item Short Form Survey (PCS SF-36v2)

[b]Primary endpoint was defined as 6 months from the baseline visit (or the time of treatment failure prior to 6 months)

[c]Median quality of life scores are represented as a dashed line

Table 1.

Participant demographic characteristics at baseline, stratified by treatment group

	Methotrexate (N=96)	Mycophenolate Mofetil (N=97)	Overall (N=193)
Sex			
Female	70 (72.9%)	59 (60.8%)	129 (66.8%)
Male	26 (27.1%)	38 (39.2%)	64 (33.2%)
Age			
Mean (SD)	38.1 (15.1)	41.6 (14.3)	39.9 (14.7)
Country			
India	60 (62.5%)	59 (60.8%)	119 (61.7%)
Australia	10 (10.4%)	7 (7.2%)	17 (8.8%)
North America	22 (22.9%)	27 (27.8%)	49 (25.4%)
Saudi Arabia	4 (4.2%)	4 (4.1%)	8 (4.1%)
Occupation			
Agriculture worker/farmer	5 (5.2%)	7 (7.2%)	12 (6.2%)
Homemaker	34 (35.4%)	36 (37.1%)	70 (36.3%)
Manual work	10 (10.4%)	7 (7.2%)	17 (8.8%)
Professional	23 (24.0%)	24 (24.7%)	47 (24.4%)
Retired	4 (4.2%)	3 (3.1%)	7 (3.6%)
Student	12 (12.5%)	9 (9.3%)	21 (10.9%)
Tradesman	5 (5.2%)	3 (3.1%)	8 (4.1%)
Unemployed	3 (3.1%)	8 (8.2%)	11 (5.7%)
Education			
Grade School	25 (26.0%)	27 (27.8%)	52 (26.9%)
Secondary/high school	39 (40.6%)	38 (39.2%)	77 (39.9%)
Undergraduate College	11 (11.5%)	12 (12.4%)	23 (11.9%)
Graduate College	12 (12.5%)	8 (8.2%)	20 (10.4%)
None	9 (9.4%)	12 (12.4%)	21 (10.9%)
Anatomical Location			
Intermediate	18 (18.8%)	22 (22.7%)	40 (20.7%)
Posterior/Panuveitis	78 (81.2%)	75 (77.3%)	153 (79.3%)
Oral prednisone at enrollment (mg/kg)			
Mean (SD)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)

Table 2.

Vision and health-related quality of life scores at baseline, the primary endpoint (6 months or treatment failure prior to 6 months), & the secondary endpoint (12 months or treatment failure between 6-12 months)

	Baseline		1° Endpoint		2° Endpoint		Wilcoxon p-value[a]		
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**0-1°**	**1°-2°**	**0-2°**
Vision-related QOL [b]									
NEI-VFQ	61.9	48.2-80.3	81.5	68.6-93.4	84.0	70.2-95.9	<0.001	0.07	<0.001
IND-VFQ	69.6	42.0-80.2	91.1	76.2-100.0	92.8	76.9-100.0	<0.001	0.02	<0.001
Health-related QOL [c]									
PCS	44.1	39.4-52.1	52.2	44.8-57.2	52.4	45.1-57.1	<0.001	0.11	<0.001
MCS	41.0	36.6-48.8	47.1	38.3-53.1	46.4	39.9-57.0	<0.001	0.99	0.002

[a] Reported p-values are from Wilcoxon signed rank tests

[b] Vision-related quality of life scales: NEI-VFQ - National Eye Institute Visual Functioning Questionnaire; IND-VFQ - Indian Vision Function Questionnaire (Indian participants only)

[c] Health-related quality of life scales: PCS - physical component score of the Medical Outcomes Study 36-Item Short Form Survey (PCS SF-36v2); MCS - mental component score of the Medical Outcomes Study 36-Item Short Form Survey (MCS SF-36v2)

Table 3.

Results from linear mixed models comparing the difference in quality of life at the primary endpoint by treatment group and by treatment success[a,b]

	A. Methotrexate (vs. Mycophenolate Mofetil)			B. Treatment Success (vs Treatment Failure)		
	Coef.	**95% CI**	**P-value**	**Coef.**	**95% CI**	**P-value**
Vision-related QoL [c]						
NEI-VFQ	2.2	−1.4-5.8	0.23	9.8	6.2-13.5	<0.001
IND-VFQ	3.9	−1.5-9.3	0.16	15.6	10.2-20.8	<0.001
Health-related QoL [d]						
PCS	0.6	−1.3-2.6	0.51	3.6	1.6-5.5	<0.001
MCS	−0.5	−3.2-2.2	0.72	3.7	1.0-6.5	<0.001

[a]Primary endpoint was defined as 6 months from the baseline visit (or the time of treatment failure prior to 6 months)

[b]All multivariable models controlled for baseline quality of life, age, sex, and site (random effect)

[c]Vision-related quality of life scales: NEI-VFQ - National Eye Institute Visual Functioning Questionnaire; IND-VFQ - Indian Vision Function Questionnaire (Indian participants only)

[d]Health-related quality of life scales: PCS - physical component score of the Medical Outcomes Study 36-Item Short Form Survey (PCS SF-36v2); MCS - mental component score of the Medical Outcomes Study 36-Item Short Form Survey (MCS SF-36v2)