Uveitides, particularly intermediate, posterior, and panuveitides, are potentially blinding diseases that typically require aggressive treatment and meticulous control of the inflammation to prevent visual loss.1 The uveitides comprise more than 30 diseases and are categorized by the primary anatomic site of inflammation as anterior, intermediate, posterior, and panuveitides. Noninfectious anterior uveitides typically are treated with topical corticosteroids, although certain diseases (eg, juvenile idiopathic arthritis–associated chronic anterior uveitis) may require immunosuppression. Many noninfectious intermediate uveitides and most noninfectious posterior and panuveitides are treated with systemic medications. Currently available data suggest that for many noninfectious uveitic diseases, immunosuppression (coupled with oral corticosteroids) results in superior outcomes and fewer corticosteroid adverse effects than oral corticosteroids alone.1 The Multicenter Uveitis Steroid Treatment trial and follow-up study demonstrated that oral corticosteroids and immunosuppression produced superior visual outcomes than a...
long-lasting regional corticosteroid therapy approach (ie, the fluocinolone acetonide implant) largely because of chorioretinal damage that occurred during periods of uveitis relapse before a reimplant of the regional therapy. Furthermore, with the strategy of adequate immunosuppression to taper prednisone to 7.5 mg/day or less, the systemic adverse effects with the systemic approach were no greater than with the regional approach, except for a greater use of antibiotics for infections. Hence this approach often is the preferred initial treatment approach for more severe uveitides.

There are 4 categories of immunosuppressive agents used in uveitis treatment: antimetabolites (eg, azathioprine, methotrexate, and mycophenolate), calcineurin inhibitors (eg, cyclosporine and tacrolimus), alkylating agents (eg, cyclophosphamide and chlorambucil), and biologics (eg, adalimumab). Because of the concerns about the long-term risk of cancer, alkylating agents now are used rarely, although they are among the most potent agents and potentially remission-inducing. The most commonly used agents are the antimetabolites methotrexate and mycophenolate. Azathioprine is tolerated less well than the other 2 antimetabolites and is used less often in the United States. Calcineurin inhibitors often are used along with an antimetabolite, as approximately 20% to 25% of patients treated for uveitis will need more than 1 immunosuppressive drug to achieve successful corticosteroid sparing (ie, suppressed [inactive] disease and prednisone, ≤7.5 mg/day).

The question that arises is whether any of the antimetabolites have greater effectiveness than the other two. One large retrospective comparative study suggested that mycophenolate was at least faster than methotrexate and perhaps superior, with a greater proportion having successful corticosteroid sparing with mycophenolate at 6 months. Azathioprine was not substantially different from mycophenolate for corticosteroid sparing but had a greater rate of discontinuation for adverse effects, whereas mycophenolate and methotrexate had similar rates of discontinuation for adverse effects. An analysis of the Systemic Immunosuppressive Therapy for Eye Disease (SITE) cohort using marginal structural models demonstrated that mycophenolate was initially faster than methotrexate but that by 9 months, both had similar effectiveness. However, in both of these studies, a dose escalation approach was prevalent: mycophenolate typically was administered at 2 g/day and escalated to 3 g/day and methotrexate at 10 to 15 mg/week and escalated to 25 mg/week, sometimes incrementally (eg, 2.5–mg/week increments every 4-6 weeks). In the retrospective study, most patients required 15 mg/week of methotrexate for uveitis control, and in the SITE study, the median effective dose of methotrexate was 12.5 mg/week (and 2 g/d for mycophenolate). Despite the success with 2 g/d mycophenolate in the SITE study, 2-year follow-up in the Mount Sinai study of posterior uveitides suggested that approximately 75% of patients treated with mycophenolate would require 3 g/day to experience successful corticosteroid sparing. More modern approaches often either initiate methotrexate at 15 mg/week and escalate to 25 mg/week in a single step if the lower dose is not adequately effective or use 25 mg/week; similarly, mycophenolate is administered at 2 g/day and increased to 3 g/day in a single step if the lower dose is not adequately effective or to just increased automatically to 3 g/day. In this context, the First-Line Antimetabolites for Steroid-sparing Treatment (FAST) research group conducted a randomized clinical trial of methotrexate vs mycophenolate as the single immunosuppressive agent for treating noninfectious intermediate, posterior, and panuveitides, the results of which are reported in this issue of JAMA. To avoid the issue of dose escalation, the authors briefly administered (for 2 weeks) a lower dose of each drug (to assess tolerability) and then increased to the maximum oral doses of methotrexate, 25 mg/week, and mycophenolate, 3 g/day. The study was powered to detect a 20% difference in proportion with treatment success at 6 months with an assumption, based on the previous data, of a superior response rate for mycophenolate. A noninferiority margin of 10% was chosen and a noninferiority result also could be determined. The trial was international and stratified by study site. The results demonstrated that methotrexate was noninferior to mycophenolate (ie, mycophenolate was not superior).

Can these results be reconciled with previous data? The clear explanation is the difference in approach, in this case dose escalation vs rapid increase to the maximum dose. In this context, the SITE data are consistent, as mycophenolate was faster using approaches that included dose escalation but methotrexate ultimately was just as effective. Because the 2 drugs appear to have a similar effectiveness, is there a reason to choose one drug over the other? One possibility is adverse effects; methotrexate had more episodes of elevated liver enzymes, serious adverse effects due to liver enzymes, and more nausea. However, like many trials, the FAST trial was powered for efficacy and not adverse effects, so there was limited statistical power to detect differences in adverse effects. Treatments often are individualized; one might choose mycophenolate for an individual with a history of liver problems and methotrexate for someone with a history of diarrhea (the most common problem with mycophenolate in clinical practice). Costs and insurance coverage also might be considered.

What about the specific uveitic entity or uveitic anatomic class? The approach to systemic treatment for uveitides has been similar across many diseases because of a lack of disease-specific data and an impression that the specific drug is less important than the immunosuppression approach. The FAST trial performed a subgroup analysis of the behavior of the 2 drugs in posterior and panuveitides vs intermediate uveitides, an analysis that was planned at the beginning of the trial, and concluded that “methotrexate was found to be more effective in patients with posterior/panuveitis.” These data should be cautiously interpreted. The investigators did not stratify by anatomic class. Therefore, randomization was lost for this subgroup analysis. Subgroup analyses for which randomization is lost are more often because of chance variation rather than true differences. The interaction P value was significant, suggesting that the behavior of the 2 drugs in this trial might be different in the 2 classes, but the results were not definitive. The difference should be viewed as exploratory and suggestive, and the authors’ conclusion in the abstract that “Further research is needed to determine if either drug is more effective based on the anatomic subtype of the uveitis” is correct. To summarize, the FAST Trial demonstrated similar effectiveness for mycophenolate and methotrexate when used at the maximum oral doses, results that should give clinicians confidence in using either treatment and individualizing therapy.