Abortion of the UVEXATE study: are we unable to evaluate cheap and well-tolerated treatments?

Sirs,

Posterior uveitis with cystic macular oedema is a serious form of ocular sarcoidosis because of visual acuity loss (1). Mainstay of treatment is systemic glucocorticoids administration, efficient in 80% of cases (1), but relapse rates approach 50% during dose tapering. To date, methotrexate, a validated corticosteroid sparing drug in pulmonaary sarcoidosis (2) as well as an affordable product (25 dollars per month), is the preferred second-line agent, but it has only been evaluated in retrospective studies regarding the ophthalmic indication (3).

The efficacy study of methotrexate to treat sarcoid-associated uveitis (UVEXATE) was the first multicentre, randomised, double-blinded, placebo-controlled clinical trial evaluating methotrexate as a first line corticosteroid sparing agent in severe sarcoid uveitis (see details on ClinicalTrials.gov). Patients first entered the study in 2009 but UVEXATE had to be stopped three years later because of insufficient inclusions. Seven patients followed the protocol to its end, 2 in the methotrexate arm, 5 in the placebo arm.

The limited rate of inclusions can be imputed to the scarcity of the condition or to a stringent methodology. Competition with off-label administration of anti-TNF alpha agents also played a role. These biotherapies are increasingly used in uveitides as an alternative to conventional immunosuppressive drugs, despite an important cost (circa 500 dollars per month) and a significant risk of serious infections (1). They have been evaluated retrospectively in refractory uveitis (1). Controlled prospective studies have just ended, with encouraging first results (4). However, they do not assess first line corticosteroid sparing effect or scrutinise patients subsets with critical visual prognosis (4). Contrarily to refractory uveitis, a rarer condition in sarcoid uveitis, severe forms of posterior uveitis mainly concern Caucasian women in their fifties (1). In this population, long-term or high-dose corticotherapy, whether effective or not, is thorny because of cardiovascular and osteoporotic comorbidities. It seems odd that specific, recent and onerous treatments enjoy evidence-based assessment for rare conditions before older, cheaper and pleiotropic ones do for more common diseases. Intriguingly, among our trial's few patients, we found a trend of lower efficiency in the methotrexate group (mean cumulated prednisone dose 6812 mg *vs.* 5565). No rescue triamcinolone injection had to be performed in the placebo group, while 1 patient out of 2 received it in the methotrexate group.

These observations buttressed our view that there is a need to determine the relevance of this economical and well-tolerated immunosuppressive drug. Funded by the Assistance Publique-Hôpitaux de Paris, France; UVEXATE Study ClinicalTrials.gov number, NCT00918554.

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