

## letter to the editor

## Bacteria-eradicating therapy for ocular adnexal MALT lymphoma: questions for an open international prospective trial

We read with great interest the article by Grünberger et al. on the 'blind' administration of doxycycline in a retrospective series of 11 patients with ocular adnexal lymphoma of MALT-type (OAL) [1]. Authors used this therapy on the basis that, in the Italian experience [2], most cases of OAL were shown to be related to chlamydial infection. However, a centralized molecular assessment of chlamydial infection was not performed, and no clinical responses were observed after a median follow-up of 9 months [1]. These results contrast with the Italian prospective trial, where doxycycline activity was assessed in 27 patients, including both Chlamydia-positive and -negative OAL. In a preliminary analysis of that trial [3], doxycycline administration has been associated with a 63% response rate in patients with Chlamydia-positive OAL (median follow-up: 24 months). One third of responses were slow and gradual, suggesting that a longer follow-up is required to properly assess doxycycline activity against OAL. Furthermore, the results reported by Grünberger et al. [1] diverge into independent reports of durable remissions in three OAL patients treated with the same 'blind' antibiotic therapy [4] and of some cases of 'spontaneous' regression of conjunctival lymphoma in Japanese patients treated with topic ofloxacin for one month after biopsy [5]. These discrepancies in therapeutic results raise several clinical and methodological questions on the management of chlamydia-related OAL, and suggest that additional clinical and laboratory prospective studies are needed to avoid potential interpretation biases, particularly those intrinsic of retrospective studies.

To elucidate some complex issues on the epidemiology and management of OAL, an open prospective phase II trial with centralized molecular analysis has just been activated. This trial, named IELSG #27, will be conducted under the sponsorship of the International Extranodal Lymphoma Study Group ([www.ielsg.org/trialsonfr.html](http://www.ielsg.org/trialsonfr.html)), and its main endpoints regard the definition of the anti-OAL activity of upfront antibiotic therapy with doxycycline and the identification of molecular genetic features potentially useful as predictors of response. Other important endpoints of this trial regards the screening of other infectious agents potentially associated with OAL. The involvement of chlamydial strains with sequence variations not recognized by current diagnostic tests or of other bacteria responsive to doxycycline is suggested by the observation that,

in the Italian prospective trial [3], one-third of patients with chlamydia-negative OAL achieved an objective lymphoma regression after doxycycline treatment. Finally, the IELSG #27 trial will produce reliable data on potential variations in the prevalence of the chlamydia-OAL association among different geographical regions. Similarly to the original Italian study [2], *Chlamydia psittaci* DNA has been detected in 78% of Korean patients with OAL [6], whereas an absence of correlation or very low prevalence values have been reported in other countries [7, 8]. Even if these discrepancies could be explained by differences in sensitivity or specificity of the detection methods used, it is important to underline that these features are in line with previous reports on HCV- and *Borrelia burgdorferi*-related lymphomas. Recently, a large retrospective study with centralized molecular analysis confirmed the existence of geographical variations in the prevalence of chlamydia-OAL association [9]. However, these features could well be due to sampling-related biases or to the presence of chlamydial DNA loads below the threshold of PCR detection due to the use of wide-spectrum antibiotics before biopsy, which is a common practice in OAL patients. In this intricate context, the conclusive demonstration of these geographical variations by the IELSG #27 trial will stimulate further studies aimed at better defining the role of epidemiological, environmental or genetic factors in OAL.

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