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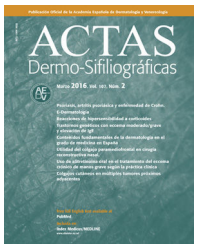

LETTERS TO THE EDITOR

The Possible Combined Action of Different Trigger Agents in Rosacea

Posible acción combinada de los diferentes agentes desencadenantes en la rosácea

Dear Editor,

We read with great interest the paper entitled ''Oral ivermectin to treat papulopustular rosacea in a immunocompetent patient.'' by Hernández-Martín[1] that prompted us to make some observations and to report our experience. The Author described a patient with papulopustular rosacea that has been considered immunocompetent but it was not specified whether laboratory examinations have been performed to investigate the immune status of the patient (as complete blood count, human immunodeficiency virus test). Moreover, the Author stated that the past medical history of the patient included topical immunomodulators, but without defining the specific drug.[1] Due to the only partial and/or transient rosacea improvement after several topical and systemic treatments, Hernández-Martín recommended a single 250 μg/kg dose of oral ivermectin leading to complete remission of the rosacea lesions.[1] However, the Author did not demonstrate by skin scraping or standardized skin surface biopsy neither the presence nor an excessive number of *Demodex folliculorum* (DF) mites in the pilosebaceous units to justify the oral antiparasitic therapy.[2] It is known that patients with papulopustular rosacea may have a higher density of DF mites on their faces than controls. However, in the absence of any qualitative and quantitative information on DF, it could be hypothesized that ivermectin may have operated through immunomodulating mechanism rather than through a true acaricidal action. The immunomodulatory effect of ivermectin has been reported long ago in mice,[3] and very recently confirmed by Schaller et al.[4] who found, in 20 Caucasian patients with moderate to severe rosacea treated with topical ivermectin for ≥12 weeks, that the gene expression levels LL-37, HBD3 and TNF-α was significantly reduced after and during treatment.

Regrettably, Hernández-Martín[1] neglected that also a DF-related bacterium, *Bacillus oleronius*, may express antigens that stimulates an inflammatory immune response[5] and that other different triggers may contribute in the pathogenesis of rosacea, more specifically gastrointestinal disorders like *Helicobacter pylori* (HP) infection and small intestine bacterial overgrowth (SIBO).[6,7] In two previous studies, we reported our experience on 60 rosacea patients that were followed up for 3 years, in which we have investigated the prevalence of three possible trigger agents: DF (through SSSB on rosacea lesions [test was considered positive for density >5 mites/cm^2]), HP infections (through urea breath test) and SIBO (through lactulose breath test).[8,9] Recently, we completed the study with a 5-year follow up. Shortly after enrolment, DF was the agent most frequently found (75%) followed by SIBO (67%) and HP infection (13%). HP infection prevailed in patients with erythrosis, SIBO in patients with papulo-pustular rosacea whereas DF was not associated with specific rosacea types. DF was found as the only trigger in 16 patients whereas 29 patients were positive for more than one trigger agent (23 patients had DF + SIBO, 4 patients DF + HP and 2 patients DF + HP + SIBO). Patients that proved positive for more than one triggering agent were treated in the following order: DF acaricidal treatment (crotamiton cream once/daily associated with azelaic acid gel once/daily for 3 weeks); antibiotic therapy for SIBO (rifaximin 1200 mg/daily for 10 days), antibiotic therapy for HP (rabeprazole 10 mg + amoxicillin 1000 mg + metronidazole 250 mg twice/daily for 2 weeks). The topical therapy for DF was effective in reducing its population and in improving the cutaneous lesions but only 26% of the patients remitted. The 23 patients positive for both DF and SIBO underwent acaricidal treatment but the majority of them (74%) remitted only after rifaximin treatment. Among the 40 exclusively SIBO positive patients treated with rifaximin, 31 remitted, 8 improved and 1 did not. Overall, most of our patients (61%), treated in accordance with the specific causal agent, cleared and had no relapsed in the following 5 years, confirming our previous studies.[8,9] In conclusion, we emphasize that the eradication of the underlying trigger agents in rosacea may be crucial in improving the disease and in maintaining the clinical remission over time. However, the search for the presence of SIBO should be done in rosacea patients since its treatment seems to be relevant in improving the disease and maintaining the clinical remission, also when more than one microorganisms are still present.

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Reply To: The Possible Combined Action of Different Trigger Agents in Rosacea

Réplica a ''Posible acción combinada de los diferentes agentes desencadenantes en la rosácea''

Dear Editor,

I thank Ciccarese et al. for their comments and welcome their thoughts about my article on the successful therapy of papulopustular rosacea in an immunocompetent patient.[1]

Rosacea is a chronic inflammatory condition diagnosed clinically. In the absence of clinical findings suggestive of any underlying comorbidity, analytical assessment or histological study is largely unnecessary.[2] Skin surface biopsy technique and skin scrapings may help visualize mites from follicular canals, but the relevance of this finding to the management of the condition is unclear and it is not routine. Nevertheless, we agree with Ciccarese et al. that ivermectin might play a role not only as an acaricide drug but also as an immunodulatory agent in controlling rosacea flares. In fact, the mechanism of action of topical immunomodulators such as pimecrolimus and tacrolimus (that proved non-efficacious in our patient) is centered on diminution of inflammation rather than antimicrobial action.[3]

Several microorganisms have been hypothesized to play a role in the pathogenesis of rosacea, but their exact role is unclear. Ciccarese and colleagues have published two studies on the role of *Demodex folliculorum*, *Helicobacter pylori* and small intestine bacterial overgrowth (SIBO)[4,5] in rosacea pathogenesis, concluding that the eradication of such underlying triggers might be crucial in improving the disease and maintaining the long-term clinical remission. However, a recent systematic review and meta-analysis found weak non-statistical significance associations between rosacea and *H. pylori* infection as well as the effect of *H. pylori* eradication on rosacea symptoms.[6] Additionally, the pathogenic role of SIBO in rosacea patients has been challenged.[7]

From a practical point of view, evidence-based therapy of rosacea is still limited and therapeutic decisions are often based on personal experiences and patient preference.[8] Although there is still a lack of randomized controlled trials, oral ivermectin has already proved useful and well tolerated in immunocompetent children with rosacea, providing long-term remission after monotherapy with one single dose.[9,10] I am aware that oral ivermectin has only been assessed for short-term safety, but these preliminary studies provide promising data about oral ivermectin as an innovative and inexpensive therapeutic approach.

Ciccarese's comments about a possible combined action of different trigger agents in rosacea are interesting and may contribute to elucidating the underlying pathogenesis of the condition. They do not however allow any definite conclusions to be drawn about the relevance of SIBO in rosacea management.

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