Long-term doxycycline and lung function in chronic obstructive pulmonary disease: A pilot observation

Sir,

The existing pharmacotherapy of chronic obstructive pulmonary disease (COPD) is targeted to bronchodilatation and not the pathogenic mechanism in which proteases, especially different matrix metalloproteinases (MMPs), play a significant role.[1] Although the inhibition of MMPs have been identified as a prospective target of therapy,[2] no new artificial anti-MMPs molecule has been available for clinical trial.

We have exploited this scope of MMPs inhibition in an ethically approved, real world, single arm, prospective, pilot observation in a cohort of our COPD patients (diagnosed on GOLD criteria)[3] through using long-term oral doxycycline as a non-specific MMPs inhibitor.[4,5] The patients selected on availability of written informed consent and been stabilized on standard pharmacotherapy (SAMA/LAMA with LABA + ICS ± SABA) were treated with long-term add-on oral doxycycline (100 mg bid orally). All the patients were co-prescribed ranitidine (150 mg 30 minutes before breakfast and dinner). The follow up and the repeat spirometry were done according to the convenience of the patients in this non-sponsored study. After a period of 2 yearsof the initiation, the records were collected over a period of 6 months and the patients with at least one repeat spirometry were taken for statistical analysis. These patients were then grouped according to the duration of receiving doxycycline as Group 1 (<100 days), Group 2 (100-400 days), and Group 3 (400-800 days). A similar and concomitant collection of data from other COPD patients (Group-4) was also done when the patients were treated with standard pharmacotherapy alone during that period and had at least one spirometry on follow up. The changes between the initial and the final post bronchodilator FEV_1 values for each group were noted and an analysis was done using the paired Student '*t*' test for both the categories of patients with (Group 1, 2, 3) or without (Group 4) add-on doxycycline.

Out of 97 prescriptions collected, only 45 patients continuing add-on doxycycline could be included since they had at least one repeat spirometry at some point of time after the initial evaluation. The numbers of patients belonging to the groups mentioned were 8, 26, 11, and 14, respectively [Table 1]. There was a universal improvement in lung function in patients receiving add-on doxycycline for different durations with significant (P = 0.00002) difference in post bronchodilator FEV_1 [Table 1] for the group 2 patients. The improvement appears as a function of duration of therapy. Apart from FEV_1, other spirometric variables have also shown concomitant improvement [Table 1]. The mean initial post-bronchodilator value of FEV_1 had improved by 80, 110, and 90 ml in group 1, 2, and 3 respectively while it dropped by 160 ml in patients on standard therapy alone [Table 1] that tallies with the natural history of the disease that has also been observed elsewhere.[6]

Table 1: The number of patients and duration of treatment with (Group-1,2,3) and without (Group-4) add-on doxycycline with the change in post bronchodilator FEV_1 with time

Duration	Group 1 <100 days	Group 2 100-400 d	Group 3 400-800 d	Group 4 >800 days
Number of patients	*n*=8	*n*=26	*n*=11	*n*=14
Duration (mean)	83.0±11.83	234.65±90.75	590.27±133.74	734.93±425.56
Age	64.38±6.78	60.77±10.82	61.82±6.69	65.43±9.90
Mean post bronchodilator FEV_1 (initial)	1.03±0.40	0.83±0.38	1.02±0.45	1.14±0.39
Mean FEV_1 post bronchodilator (after add-on doxycycline)	1.11±0.47	0.94±0.40	1.11±0.45	0.98±0.42 (-160 ml)
Improvement in post bronchodilator FEV_1	(80 ml)	(110 ml)	(90 ml)	(-160 ml)
Significance of the change (*P* value)	0.252	0.000020	0.082	0.0734

FEV_1: Forced expiratory volume in the first one second (expressed in liters)

Conceptually, the study remains unique with a strong translational element in exploiting an altogether new concept of the anti-MMPs property of doxycycline in a chronic debilitating condition like COPD. Incidentally, this low-cost and well-tolerated antibiotic[7,8] has been available for over 30 years in the market with experience of many long-term uses.[9-12] It also has an USFDA approval for use in periodontal disease in line of exploiting the property of MMPs inhibition. The agent has widely been in use as an antibiotic and has shown significant reduction of MMP-9 activity and concomitant elastin degradation *in vitro*.[13] Another study shows improvement of the lung function in a cohort of stable Gold II COPD patients on treatment with doxycycline (100 mg OD) for 1 month.[14]

Our observation has many implications as regards the future research and development of practice policy for COPD. A properly conducted double-blind placebo controlled trial in one hand and serious basic research

to demonstrate the actual effect of such treatment on the pathogenesis of the disease and remodeling on the other are essential. Subject to further validations of our observation, the impact may extend to make altogether a paradigm shift in the treatment policy of the disease in future as the MMPs inhibition in COPD appears to change the natural history of this relentlessly progressive disease for which the researchers are looking for an answer.

The study has several weaknesses. Methodologically, it is weak with lack of regular follow up and assessment on a defined and formatted protocol, absence of tolerance report on long-term use of doxycycline, non-inclusion of other assessment parameters (6MWT, SGRQ etc) but just spirometric lung function variables, and for no attempts, what so ever, for the proof of concept.

Pending the verification of the results through an appropriately designed clinical trial, the agent cannot be recommended for use in clinical practice.

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