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Impact of long-term doxycycline on lung function & exacerbations: A real-world open, prospective pilot observation on chronic obstructive pulmonary disease

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***Background & objectives*: Upregulation of matrix metalloproteinases (MMPs) is related to the pathogenesis of chronic obstructive pulmonary disease (COPD). We aimed at assessing the tolerability and impact of long-term use of MMP inhibitor doxycycline in COPD.**

***Methods*: A cohort of COPD patients was randomized to continue a uniform COPD treatment with or without add-on long-term oral doxycycline. The lung exacerbations (spirometry), adverse events and health status (COPD Assessment Test score) were noted at 3, 6, 9 and 12 months of therapy. Measurement of the serum MMP-2, and 9 and high-sensitive C-reactive protein (hs-CRP) levels was done at the start of the study and at three months, whenever possible.**

***Results*: There were 27, 19, 13 and 10 patients with add-on doxycycline group and 22, 19, 11 and 7 patients with COPD treatment alone at 3, 6, 9 and 12 months of treatment respectively. The improvement was obvious and mostly (at 6 and 12 months) significant (P>0.05) for lung function parameters [forced expiratory volume in one second (FEV_1), FEV_1/forced vital capacity (FVC) and forced expiratory flow at 25-75% of FVC (FEF_{25-75})] and universal for health status at all measurements, with an overall 26.69 per cent reduction in exacerbations. The analysis with the lung function changes in the available population with protocol violation also supported the same trend. The concomitant reduction in serum MMP-9 (P=0.01), MMP-2 (P=0.01) and hs-CRP (P=0.0001) levels (n=21) at three months was also significant. The adverse reactions with add-on doxycycline appeared acceptable.**

***Interpretation & conclusions*: Long-term doxycycline appears well tolerated and seems to improve lung function, health status and exacerbations in COPD. The claim needs further scientific validations.**

Key words COPD - emphysema - MMP - quality of life - respiratory function tests

Chronic obstructive pulmonary disease (COPD), a disease of the airways with systemic inflammation, is characterized pathologically by narrowing and remodelling of the airways with or without mucus hypersecretion and/or destruction of the alveolar membranes[1]. Physiologically, there is progressive and poorly reversible airflow limitation with decreased vital and diffusion capacities. Clinically, the patients suffer from progressive and relentless shortness of breath with or without cough and expectoration but with a myriad of systemic manifestations. Incidentally, COPD shows a rise in prevalence globally causing more than three million deaths annually[2]. The treatment of COPD till date is largely symptomatic with bronchodilators without addressing the pathogenesis that includes the participation of matrix metalloproteinases (MMPs) as a major mediator[3]. Thus, MMP inhibition has been regarded as a potential therapeutic target[4]. This illusive target was evaluated through an open, prospective, real-world observation in a cohort of COPD patients with long-term (12 months) use of oral doxycycline, a known MMP inhibitor[5,6]. The objective of this intervention was to note the effect on spirometric lung functions, health status in terms of COPD Assessment Test (CAT) score and exacerbation frequency along with tolerability of such use of doxycycline. The impact on systemic inflammation [high-sensitivity C-reactive protein (hs-CRP)] and serum MMP-2 and MMP-9 levels were also checked for at three months of interventions.

Material & Methods

The study was carried out at the department of airway diseases, Institute of Pulmocare & Research, Kolkata between April 2011 and January 2015 on a real-world protocol approved by the Institutional Ethics Committee. The protocol was prospectively registered with Clinical Trial Registry of India (CTRI/2011/07/001873).

Selection, evaluation and inclusion of the participants: Patients with COPD (age: 40–75 yr, GOLD Stage II and above), diagnosed on the basis of GOLD guideline through spirometry (observing the ATS/ERS principles)[7], were selected with a written informed consent from the Outpatient department of the institute. Patients unwilling to join, having any other concomitant and significant pulmonary problem or systemic co-morbidity, having history of exacerbation or any active or suggestive respiratory tract infection in the preceding six weeks were excluded. Individuals with active smoking, known doxycycline intolerance and premenopausal state were also excluded. One hundred and thirty-four participants were screened; of whom, 88 participants were randomized. Forty-six participants were excluded [loss to follow up=14, unwilling to join=9, showed reversibility=20, serious adverse event (SAE)=1 and unknown reason=2].

Treatment and assessment protocol: All the patients were offered a uniform COPD pharmacotherapy with combination of inhaled short-acting β2-agonist (salbutamol)+short-acting anti-muscarinic agents (ipratropium bromide) with inhaled long-acting β2-agonist (formoterol)+inhaled corticosteroid (budesonide). Alongside the rescue use of short-acting β2-agonist, medications for other co-morbidities were also prescribed. The patients were re-evaluated with spirometry and CAT score[8] on follow up after six weeks of stabilization period. Thereafter, the participants were randomized using a random number table into two arms as (*i*) those with continuation of the ongoing COPD treatment alone and (*ii*) those with add-on oral doxycycline to the same COPD therapy. The add-on doxycycline was offered as 100 mg tablets of doxycycline hyclate (DOXT S-100, Dr Reddy's Laboratories, Hyderabad) as once or twice daily (to be consumed after one hour of food) for having a body weight of below or above 40 kg. The side effects (sure or suspected) and exacerbation events (as per the Aspen Lung Conference criteria)[9], if any, were assessed every three months and also through telephonic enquiry.

The measurement of matrix metalloproteinases (MMPs) and high-sensitivity C-reactive protein (hs-CRP): Serum was separated from the blood (4 ml) of the patients as and when available at the start of the randomization and after three months. The serum samples were utilized to measure MMP-2 and MMP-9 levels using commercial ELISA kits (Quantikine ELISA Kit; R&D Systems, USA) as per manufacturer's instructions. The assays employed a quantitative sandwich enzyme immunoassay technique designed to measure total MMPs (pro and active form). Simultaneous measurement of the hs-CRP was done by immunoturbidimetric method using a commercial kit (Randox, UK).

Details of assessments at follow up: The patients were followed up every three months (90±30 days) as per the protocol with repeat spirometry and measurement

of the CAT score at each visit along with recording of the exacerbation events and adverse reactions, if any. Serum MMP-2, MMP-9 and hs-CRP were measured whenever the patients agreed to allow the collection of blood during the first three months of follow up. Before compilation of data, a detailed enquiry was made with each patient violating the protocol.

Statistical analysis: At the fourth follow up visit (one year) of the initiation of the trial (from April 2011 to August 2015), the protocol was closed informing all the patients recruited. All the available data were pooled together and analyzed statistically for the spirometric values and CAT score. The intragroup and intergroup comparisons at each visit were made based on the difference in the values as compared to baseline of the respective patients. The biochemical values for hs-CRP and MMP (MMP-2) levels were also compared similarly. GraphPad Prism version 5 (GraphPad Software, Inc. San Diego, California, USA) was used for applying the paired Student's t tests for the comparison, and $P<0.05$ was considered statistically significant. Finally, an intention-to-treat analysis was added with available data. The exacerbation events recorded were also compared between the two groups.

Results

Out of 134 participants that were screened, 88 patients were included in the study using a randomization table (meant for 300; Fig. 1). While 54 patients were allocated for add-on doxycycline regimen, 34 patients continued on the ongoing COPD treatment alone (Fig. 1). The two groups were similar as regards to age (P=0.2), body mass index (P=0.8) and forced expiratory volume in one second (FEV_1) (P=0.7) (Fig. 1). The number of patients at the end of 3, 6, 9 and 12 months of follow up visits were 27, 19, 13 and 10 and 22, 19, 11 and 7, respectively, in the add-on doxycycline and COPD treatment alone arms (Fig. 1 and Table I).

The spirometric variables [FEV_1/forced vital capacity (FVC), FEV_1 and forced expiratory flow at 25-75% (FEF_{25-75})] displayed a global and consistent improvement in airflow limitation in patients with add-on doxycycline group, and it appears time dependent and often significant (Tables I and II). The absolute changes in FEV_1 were 90, 93, 155 and 170 ml and that of FEF_{25-75} were 100, 80, 210 and 230 ml, respectively, at 3, 6, 9 and 12 months of follow up. There was an overall 26.69 per cent reduction of

Table I. Comparison of change (intragroup) in different spirometric parameters and chronic obstructive pulmonary disease assessment test score at different points of follow up with exacerbation events in patients with chronic obstructive pulmonary disease therapy alone and chronic obstructive pulmonary disease therapy with add-on doxycycline

Add-on doxycycline group	3 months (n=27)		6 months (n=19)		9 months (n=13)		12 months (n=10)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
CAT score	11.54	8.5***	11.06	7.89***	10	6.83**	9.27	6.64***
FEV_1 (post-BD)	1.06±0.51	1.11±0.57	1.01±046	1.103±0.56	1.09±0.50	1.249±0.61**	1.17±0.54	1.37±0.67**
FEV_1/FVC (post-BD)	49.30±10.89	51.59±12.07*	47.37±11.55	50.05±11.76*	49.06±11.78	54.96±13.92*	50.46±13.06	56.30±13.23**
FEF_{25-75} (post-BD)	0.53±0.29	0.63±0.41**	0.52±0.27	0.60±0.43	0.56±0.29	0.77±0.59**	0.61±0.31	0.84±0.51**
Exacerbation n (%)	5 (18.52)		4 (21.05)		1 (7.69)		2 (20)	
COPD therapy alone	3 months (n=22)		6 months (n=19)		9 months (n=11)		12 months (n=7)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
CAT score	11.5	10.68	10.68	10.68	10.9	10	11	11
FEV1 (post-BD)	0.96±0.39	1.01±0.36	1.021±0.34	1.063±0.37	0.92±0.33	0.91±0.36	0.82±0.26	0.81±0.32
FEV_1/FVC (post-BD)	51.04±11.91	52.75±10.15	52.68±11.82	54.53±10.19	53.67±13.60	56.05±15.54	53.99±13.16	53.24±16.60
FEF_{25-75} (post-BD)	0.52±0.22	0.53±0.26	0.54±0.23	0.58±0.24	0.50±0.19	0.56±0.29	0.46±0.19	0.47±0.21
Exacerbation n (%)	8 (36.36)		3 (15.79)		2 (18.18)		0 (0)	

The changes in the values of CAT score and post-bronchodilator spirometric variables (FEV_1, FEV_1/FVC and FEF_{25-75}) over quarterly follow up for one year; COPD, chronic obstructive pulmonary disease; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEF, forced expiratory flow; BD, Bronchodilator. P *<0.05, **<0.01, ***<0.001

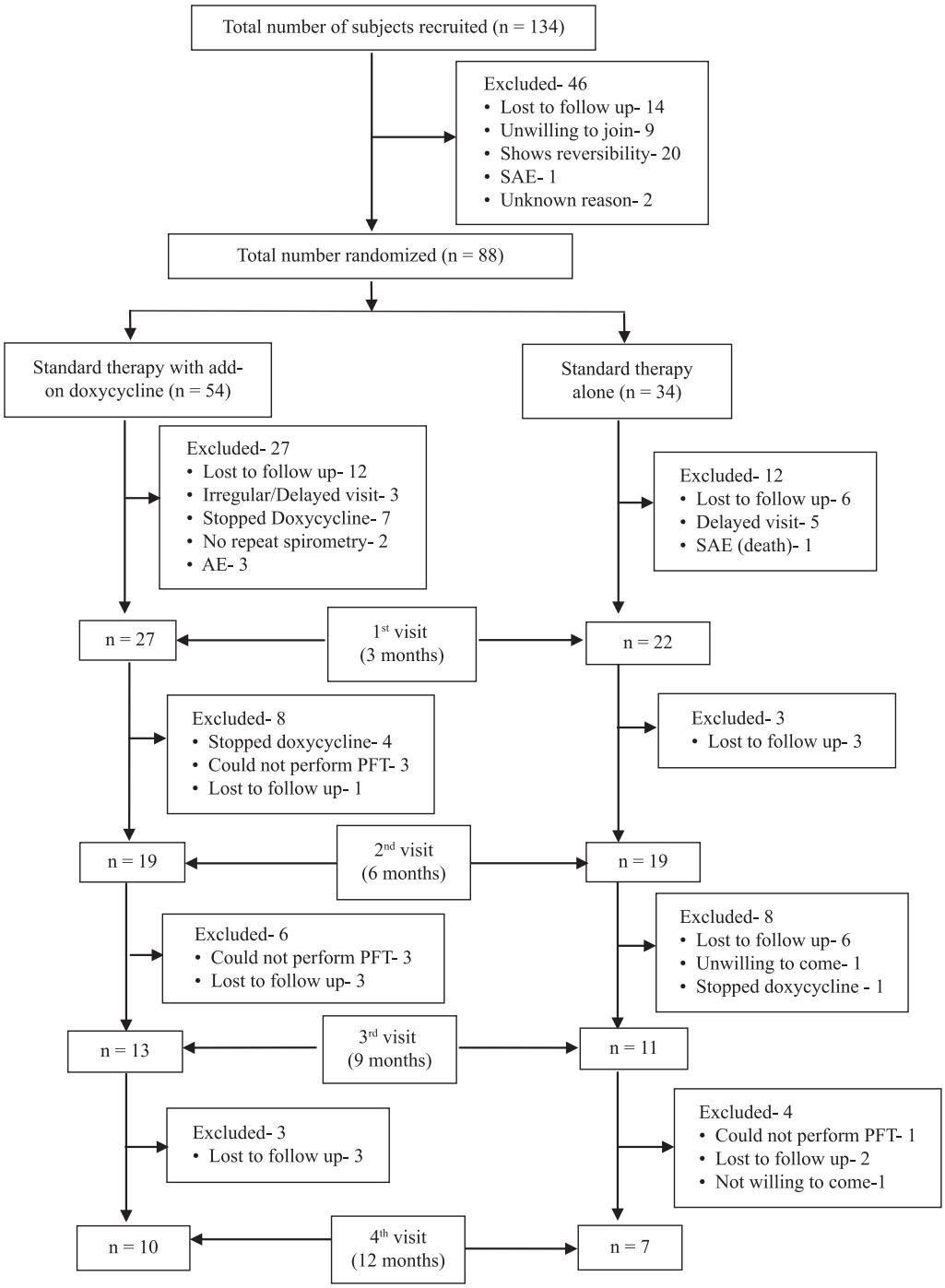

Fig. 1. Flowchart showing the number of patients in each arm at different points of time with the reasons for dropout. The inequality in the number in the two arms is discussed in test. There is no significant difference with respect to age, BMI and FEV_1 (P>0.05) in either group of recruited patients. FEV_1, forced expiratory volume in one second; BMI, body mass index.

exacerbations in the add-on doxycycline-treated group (9 patients in the experimental group as compared to 11 in the COPD treatment alone group) (Table I) with consistent and serial improvement of health status (CAT score) (Table I and Fig. 2). Doxycycline was overall well tolerated (Tables I and II).

At three months, a parallel and significant decrease in serum MMP-2 (P=0.01), MMP-9 (P=0.01) and hs-CRP levels (P=0.0001) was observed in the patients (n=21) with add-on doxycycline group as compared to no change (n=17) in COPD treatment alone group (Table III and Fig. 3).

Table II. Comparison of change (intergroup) in different spirometric parameters after treatment with COPD therapy alone and with add-on doxycycline at different points of follow up

Parameter	The difference achieved							
	At 3 months		At 6 months		At 9 months		At 12 months	
	COPD treatment	Add-on doxycycline + COPD treatment	COPD treatment	Add-on doxycycline + COPD treatment	COPD treatment	Add-on doxycycline + COPD treatment	COPD treatment	Add-on doxycycline + COPD treatment
FEV_1/FVC	1.70±6.38	2.29±4.47	1.84±6	2.68±4.85	2.38±9.6	5.9±8.45	−0.74±8.41	5.84±5.42
FEV_1 (L)	0.048±0.21	0.049±0.15	0.04±0.16	0.087±0.19	−0.01±0.17*	0.15±0.18	−0.01±0.12	0.19±0.17*
FEF_{25-75} (L)	0.015±0.14	0.09±0.18	0.04±0.14	0.08±0.22	0.06±0.21	0.21±0.36	0.008±0.10	0.22±0.24*

*P<0.05

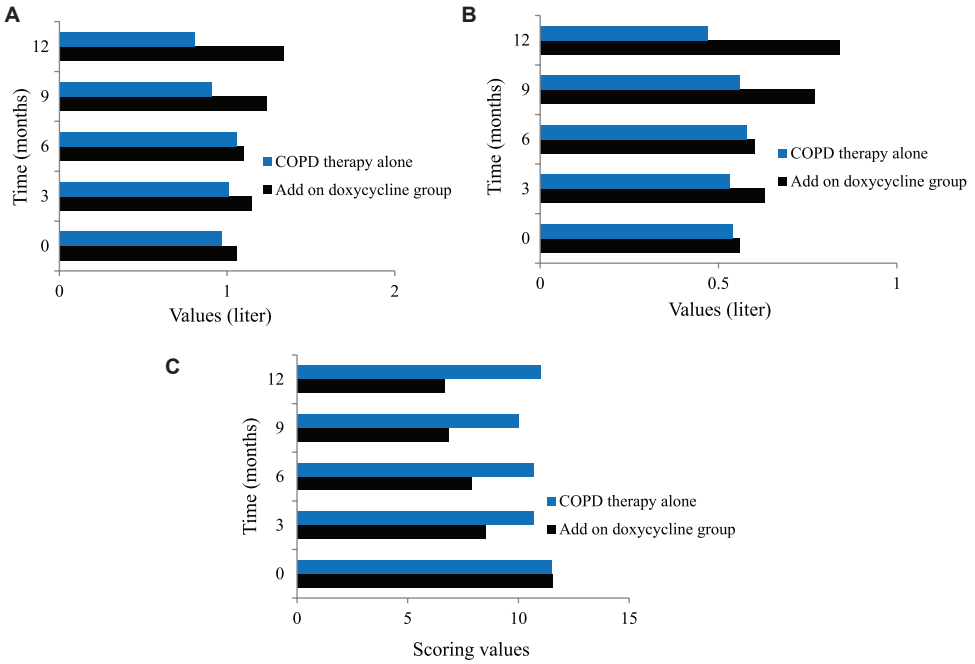

Fig. 2. Change in FEV_1 (**A**), FEF_{25-75} (**B**) and CAT score (**C**) (in X axis) from left to right in both the groups of patients (dark: add-on doxycycline and shaded: standard therapy alone) over the duration of observation expressed in Y-axis at randomization '0' and at 3, 6, 9 and 12 months of follow up.

The results of this study were further supported by the analysis of intention to treat. It showed no difference between the two groups demographically (Table IV) but a sure improvement in the absolute values of FEV_1 and FEF_{25-75} (Table IV) with a gradual upward trend from three months onwards (Fig. 2).

The protocol violations in terms of on and off discontinuation were found mostly within the first three months of randomization. On enquiry, it was mostly because the patients were made apprehensive to continue the drug (an antibiotic) for such a long time by friends, local pharmacists, some other medical practitioners *etc*. The available repeat spirometry in some of these patients (n=7 for each group) revealed that the patients who had consumed doxycycline even for a relatively short duration (141.3±110.9 days) as an add-on had an overall trend of improvement with a lesser decline in spirometric variables compared to those who remained on COPD treatment alone beyond the point of dropout (Table V).

Discussion

An improvement in lung function, exacerbation rate and CAT score in the patients receiving

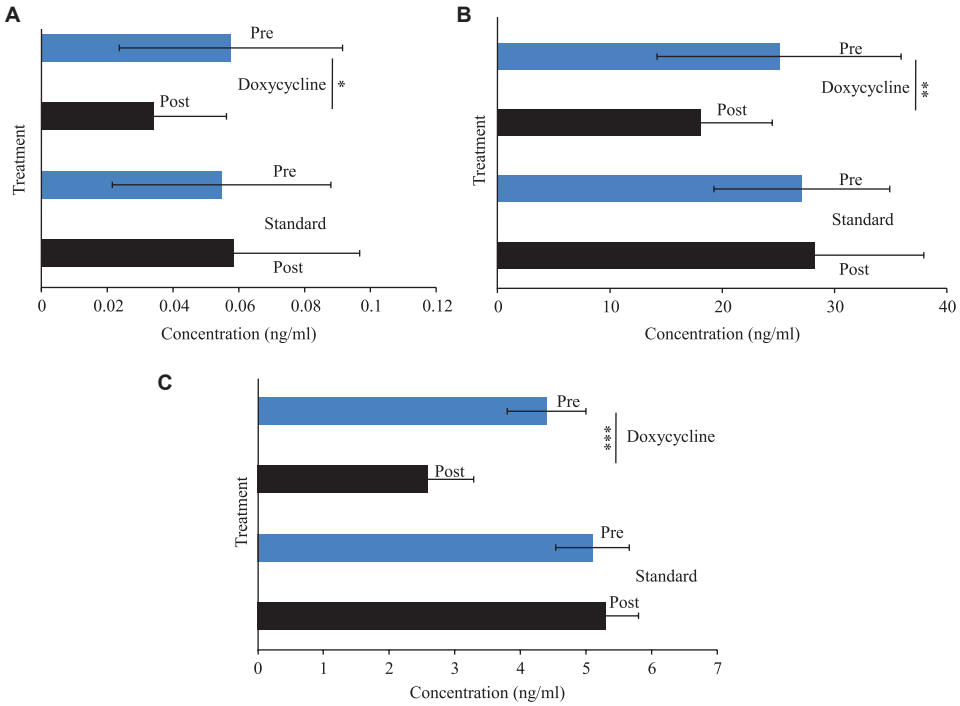

Fig 3. The comparative change in MMP-2 (**A**), MMP-9 (**B**) and hs-CRP levels (**C**) in the patients receiving COPD therapy alone and the patients on COPD therapy with add-on doxycycline ('pre' and 'post' denotes pre- and post-treatment values). MMP, matrix metalloproteinase; COPD, chronic obstructive pulmonary disease; hs-CRP, high-sensitive C-reactive protein. *P* *<0.05, **<0.01, ***<0.001.

long-term add-on doxycycline (Table I) was the consistent observation in this study. The parallel improvement in all the parameters of airflow limitation such as FEV_1, FEV_1/FVC and FEF_{25-75} across the length of follow up period suggests a reversal of obstruction in both the relatively large and the small airways. Interestingly, even in the cases of protocol violation, doxycycline carried a protracted positive impact for roughly three years of the point of dropout.

One can also infer a possible improvement in airway remodelling from the results if one extrapolated the concept of considering FEV_1/FVC ratio as a surrogate marker of remodelling in asthma[10]. Furthermore, the findings are supported by the observed change in available lung function in patients who dropped out (Table V) and also in our intention-to-treat analysis (Table IV and Fig. 4).

The observed reduction in MMP-2 and MMP-9 along with the hs-CRP level in the paired samples at three months in the add-on doxycycline group indicates towards inhibitory impact of doxycycline on MMPs and inflammation (Table III and Fig. 3).

The relentless airway and systemic inflammation in COPD associated with reduction in lung function, increase in exacerbation frequency and development of co-morbidities leads to increased morbidity and mortality among the sufferers. Conventionally, the treatment of COPD includes bronchodilatation with inhaled anti-muscarinic agents plus/minus inhaled β2-agonists and often with inhaled corticosteroids, the anti-inflammatory role of which is debatable[11]. The presently available treatment regimes do little to address the inflammation and remodelling in COPD and inhibition of MMPs has been one such potential targets for treatment.

The MMPs (class of zinc endopeptidases) have been found to play an important role in the pathogenesis of COPD[12]. Secreted by cells such as macrophages and neutrophils, this class of proteases is involved in inflammation, mucus hypersecretion and profibrotic pathways[2,13] to result in matrix remodelling. The upregulated status of MMPs in COPD in sputum, plasma, bronchoalveolar lavage and lung tissue is well reported put in the context of smoking[14]. MMP-9 and MMP-9/TIMP (tissue inhibitors of metalloproteinases) levels have been found to be higher in patients of COPD. Also, FEV_1 level has been reported to be inversely related to the increased MMP-9 level in both COPD patients and respective controls[15]. Therefore,

Table III. Change in matrix metalloproteinases (MMP)-2 and -9 levels and high-sensitive C-reactive protein with or without add-on doxycycline

Parameter	Add-on doxycycline group		COPD therapy group	
	3 months (n=21)		3 months (n=17)	
	Before Rx	After Rx	Before Rx	After Rx
Serum MMP-2	0.057±0.03	0.034±0.02**	0.054±0.03	0.058±0.03
Serum MMP-9	25.08±10.8	18.03±6.4**	27.08±7.8	28.19±9.7
Serum hs-CRP	4.4±0.6	2.6±0.69***	5.1±0.56	5.31±0.49
Number of exacerbations	-	3	-	5

The actual changes in the level of MMPs and hs-CRP with number of exacerbations. MMP, matrix metalloproteinase; hs-CRP, high-sensitive C-reactive protein. *P* **<0.01, ***<0.001

Table IV. Intention-to-treat analysis: Demographic and spirometric comparisons both intragroup (patients with COPD treatment alone or along with and inhaled corticosteroid, as A vs. B/C/D/E) and intergroup (between X vs. Y for FEV, FEV./FVC and FEF 25-75)

		Standard therapy		Add-on doxycycline	
No. of patients (n)		34		54	
Male: female		33:1		49:5	
Age (yr; mean±SD)		64.26±5.25		60.68±10.02	
Height (cm; mean±SD)		1.64±0.07		1.65±0.07	
Weight (kg; mean±SD)		60.76±11.38		61.46±9.44	
BMI (mean±SD)		22.38±3.77		22.47±3.57	
Parameter	At randomization (A)	3 months of treatment (B)	6 months of treatment (C)	9 months of treatment (D)	12 months of treatment (E)
FEV_1/FVC post-BD					
Standard therapy (n=34) (X)	50.04±12.67	52.74±8.09***	53.95±11.25***	54.71±10.70***	52.80±9.05*
Add-on doxycycline (n=54) (Y)	49.95±11.71	51.59±12.07***,#	53.11±9.14***	54.21±11.31**	58.05±9.59***
FEV_1 post-BD					
Standard therapy (n=34) (X)	0.97±0.38	1.01±0.28***	1.01±0.38***	0.93±0.29**	0.94±0.32***
Add-on doxycycline (n=54) (Y)	1.06±0.43	1.05±0.33***,#	1.13±0.36***,###	1.26±0.38***,###	1.30±0.46***
FEF_{25-75} post-BD					
Standard therapy (n=34) (X)	0.54±0.30	0.53±0.21**	0.60±0.29***	0.55±0.20***	0.72±0.56**
Add-on doxycycline (n=54) (Y)	0.56±0.30	0.59±0.26***,#	0.66±0.27***	0.78±0.35**,###	0.93±0.64***,###

Demographic characteristics of the participants with the change in the intragroup and intergroup values of FEV_1/FVC, post-bronchodilator FEV_1 and post-bronchodilator FEF_{25-75} in intention-to-treat analysis. BD, bronchodilator. *P* *<0.05, **<0.01, ***<0.001 for intergroup comparison; *P* #<0.05, ##<0.01, ###<0.001 for intragroup comparison

inhibition of MMPs can be a potential therapeutic target in COPD. Several synthetic anti-MMPs are presently under evaluation, but none has successfully passed the Phase III human trial so far[16, 17].

Doxycycline, a synthetic tetracycline derivative, has shown a significant reduction of MMP-9 activity and concomitant elastin degradation *in vitro*[18]. Moreover, doxycycline was found to possess an anti-inflammatory, antioxidant and anti-MMP role in COPD[19]. The findings of the present study also suggest that the improvement in lung function and quality of life in COPD patients can be attributed to the above-mentioned effects of doxycycline. So, the potential therapeutic role of long-term doxycycline, in addition to its traditional antibiotic effect, warrants further attention[19]. In periodontal disease, the USFDA has approved the use of doxycycline as a MMP inhibitor[20]. Hence, an ethical approval of a trial of long-term doxycycline seems justified in COPD[21-23].

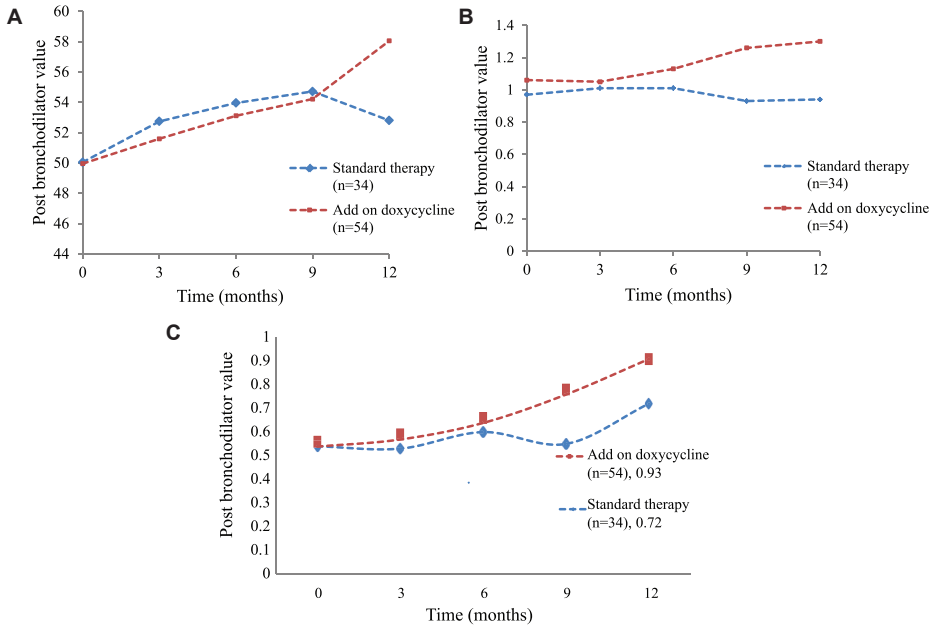

Fig. 4. The change of FEV_1/FVC **(A)**, post-bronchodilator FEV_1 **(B)** and post-bronchodilator FEF_{25-75} **(C)** over the duration of observation from randomization (marked as '0' to 3, 6, 9 and 12 months) on intension-to-treat analysis.

Table V. Analysis of lung function change of the dropout cases

Spirometric parameters	Group I (add-on doxy)	Group II (COPD alone Rx)
Total number of patients (n)	7	7
Total duration (mean±SD) in days	1265.71±463.58	1164±483.52
Duration between randomization and dropout point (mean±SD) in days	141.3±110.9	210.6±44.4*
FEV_1		
At randomization	1.23	1.09
At dropout	1.28	1.12
At latest follow up	1.14	0.95
Difference between randomization and latest follow up	−90 ml	−140 ml#
FEV_1/FVC		
At randomization	0.53	0.53
At dropout	0.58	0.57
At latest follow up	0.59	0.5
Difference between randomization and latest follow up	0.068#	−0.0258
FEF_{25-75}		
At randomization	0.6	0.58
At dropout	0.73	0.69
At latest follow up	0.64	0.46
Difference between randomization and latest follow up	0.04	−0.12#

The changes in lung function in term of FEV_1, FEV_1% and FEF_{25-75}. *P<0.05, group I compared to group II; #P<0.05 at randomization as compared to at latest follow up

A study used doxycycline for one month in stable COPD and revealed a significant improvement in lung function and C-reactive protein levels with no change in clinical status in the MRC scale[24]. Another

long-term real-world observation with doxycycline in COPD showed improvement in lung function[25]. Another study which employed roflumilast along with doxycycline in COPD for a year showed no improvement in the St. George's Respiratory Questionnaire (an equivalent of CAT score) with a reduction in the exacerbation rate only in GOLD Stage IV patients[26], suggesting that doxycycline alone may be a better option.

The observed positive effects with add-on long-term doxycycline in our COPD patients seem unlikely due to the antibiotic effect of doxycycline as the patients with suspicion of infection were excluded at randomization. The reduction in exacerbation with add-on doxycycline needs special attention as exacerbations have been found to adversely influence the survival[27], lung function[28] and quality of life[29]. This finding needs further scientific probing and long-term prospective observation.

The study, however, has several weaknesses. The power of the study was compromised due to limited recruitment and high dropout rate. In effect the recruitment in both the arms was unequal, also this could be due to the use of a randomization table for 300 patients. Since this target was difficult to achieve within a stipulated of time by a single centre, the study with the mode of randomization employed has been wrapped up as Phase I. There was also a high rate of protocol violation largely due to the inability to support the incidental expenses (travel, cost of investigations, *etc*.) and effectively counter the negative feedback in the real world for the long-term use of an antibiotic by several authorities. Follow up of the dropped outpatients with spirometry was also limited due to lack of influence on the patients. Thus, the real-world element integrated automatically to our observation has, strengthened our claim as a higher importance is often assigned to real-world trials for assessment of effectiveness[30].

Overall, it appears that the use of long-term add-on doxycycline in COPD is well tolerated and is likely to influence positively the natural course of COPD. However, further trials are required to strengthen these findings in early stages of COPD, also the use of long-acting muscarinic antagonists (LAMA) or LAMA-long-acting beta-antagonists (LABA) combination as primary bronchodilator therapy with or without doxycycline needs to be looked for.

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