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Montelukast and emotional well-being as a marker for depression: Results from 3 randomized, double-masked clinical trials

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To the Editor:

Recent articles in the press have raised questions regarding suicide as a complication of montelukast therapy.[1] The ability to determine depressive episodes or suicide related to drug therapy in uncontrolled postmarketing surveys can be difficult. Accordingly, we reviewed 3 randomized, double-masked, controlled trials conducted by the American Lung Association Asthma Clinical Research Centers (ALA-ACRC) that included montelukast as a treatment assignment to determine whether there was any signal suggesting an effect of montelukast on emotional well-being.[2,3] A total of 1469 patients were enrolled. Of these, 569 patients were randomly assigned to treatment with montelukast. Of these patients, we had follow-up data on emotional well being for 1352, of whom 536 were assigned to montelukast (Table I). The patients were 26% to 40% males, and 30% or more were minorities. In these trials, we examined measures of quality of life that included scales of emotional well-being. Herein we review the effects of montelukast on emotional status.

In the first trial, Trial of Asthma Patient Education (TAPE), 480 patients were enrolled, of whom 239 were assigned to montelukast for 4 weeks (Singulair; Merck & Co, Whitehouse Station, NJ) ; 24% of patients were between 18 and 25 years of age (ALA-ACRC, unpublished data, March 2008). In the second trial, Leukotriene or Corticosteroid or Corticosteroid-Salmeterol (LOCCS),[2] 500 patients were enrolled, of whom 165 were assigned to montelukast. Of the 500 patients, 108 were between the ages of 15 and 25 years, and 96 were children (mean age, 11 years; range, 6-14 years). Of the children, 32 were assigned to montelukast. The treatment duration was 16 weeks. In trial 3, Effectiveness of Low Dose Theophylline as Add-On Therapy for Asthma (LODO),[3] 489 patients were enrolled, of whom 164 were assigned to montelukast for 24 weeks; 20% of patients were between the ages of 15 and 25 years. The adult and children dosages of montelukast were respectively 10 and 5 mg daily. In the 3 trials, measures of the quality of life of the adults and the children were assessed by using the Juniper Mini Asthma Quality of Life Questionnaire[4] and the Juniper Paediatric Asthma Quality of life Questionnaire,[5] respectively. Scores for the Asthma Quality of Life Questionnaire (AQLQ) were obtained at baseline and at different periods, which allowed to measure changes in the emotional well-being dimension of the score. In the TAPE trial, we used the SF-36 questionnaire[6] at baseline and after 2 and 4 weeks of treatment to obtain mental component scores. We also evaluated the patients in the TAPE trial for depression at baseline by using the Center for Epidemiological Studies Depression Scale (CES-D), which measures and scores symptoms

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of depression.[7] This allowed us to calculate the correlations between the CES-D scores and measures of emotional well-being obtained from the Juniper Mini Asthma Quality of Life Questionnaire and the SF-36 mental scores. Statistical analysis was performed on the basis of treatment assignment (intention to treat) by using linear regression models.

Univariate analyses using the 3 measures of emotional well-being obtained from TAPE patients at baseline showed that the Juniper Mini Asthma Quality of Life emotional dimension scores were well correlated with the CES-D depression scores ($r = –0.44$; $P < .0001$; $N = 480$), and that SF-36 mental score correlated even better with CES-D depression scores ($r = –0.63$; $P < .0001$; $N = 480$). The latter results were similar to those reported by Hann et al.[8] Therefore, we are reasonably confident in our ability to use the Juniper AQLQ emotional dimension scores and the SF-36 mental component score as indicators of emotional well-being and depression in the aforementioned 3 trials.

Table I shows that there was no evidence of any significant deterioration of emotional well-being as measured by the Juniper AQLQ in any of the 3 trials, either in the adults or the children who received montelukast, nor were there differences among treatment groups. This was true for the adults who were followed for 2 to 24 weeks, and for the children who were followed for 4 to 16 weeks. On the contrary, we observed a positive effect of montelukast compared with the placebo group on the emotional dimension of the Mini AQLQ in the TAPE[2] trial after 2 weeks of treatment that did not persist. Similarly, when SF-36 mental component score was used as an index of well-being in the TAPE[2] trial, we observed a greater increase with montelukast after 2 weeks, and no significant difference after 4 weeks. We saw no evidence of a different effect when we limited our analysis to patients younger than age 26 years. In the 3 trials, we have no adverse event reports of psychiatric disturbances, suicide, or depressive episodes in any of the patients receiving montelukast.

These findings lead us to conclude that despite the recent publicity regarding the adverse effects of montelukast on suicide or emotional well-being, we did not find evidence to suggest that this is a general concern. We acknowledge that despite the strength of having randomized comparison groups, there are certain limitations: (1) our quality of life instruments were not directly designed to evaluate depression even though we found good correlation between our measures of well being and recognized measures of depression; (2) patients participating in clinical trials may be excluded for significant psychiatric illness; (3) our studies up to 24 weeks cannot exclude long-term effects; and (4) younger children may be more vulnerable,[9] and our trials included a small number of children, all over the age 5 years.

In conclusion, we did not find evidence of a negative effect of montelukast on emotional well being in any of the 3 ACRC trials. Although our review of ACRC trial data is reassuring, we obviously cannot exclude the possibility of idiosyncratic reactions to montelukast.

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TABLE I

Quality of life scores from 3 American Lung Association ACRC trials (means ± SEs)

	TAPE		LOCCS[2]			LODO[3]		
	Montelukast	**Placebo**	**Montelukast**	**Fluticasone**	**Fluticasone-salmeterol**	**Montelukast**	**Placebo**	**Theophylline**
Juniper Mini Asthma Quality of Life								
N, adults[§]	235	233	130	126	124	139	138	131
Baseline emotional dimension (↑, 1-7)	5.1 ± 0.1	5.2 ± 0.1	5.8 ± 0.1	5.7 ± 0.1	6.0 ± 0.1	4.0 ± 0.1	4.1 ± 0.1	4.1 ± 0.1
Change at 2 wk	0.7 ± 0.1	0.4 ± 0.1[*]	—	—		—	—	—
Change at 4 wk	0.6 ± 0.1	0.5 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1			
Change at 16 wk[‡]			–0.1 ± 0.1	0.0 ± 0.1	–0.1 ± 0.1			
Change at 24 wk	—					1.0 ± 0.1	0.8 ± 0.1	0.6 ± 0.1
N, children (ages 6 to 14 y)			32	35	29			
Baseline emotional dimension (↑, 1-7)[§]			6.3 ± 0.1	6.7 ± 0.1	6.5 ± 0.1	—	—	—
Change at 4 wk	—		0.0 ± 0.1	0.0 ± 0.1	0.3 ± 0.1[†]			
Change at 16 wk[‡]			0.4 ± 0.1	0.2 ± 0.1	0.2 ± 0.1			
Short Form-36 mental score								
N[§]	234	233						
Baseline mental score (↑, 0-100)	49.1 ± 0.7	50.8 ± 0.6						
Change at 2 wk	1.8 ± 0.5	–0.2 ± 0.5[*]	—	—	—	—	—	—
Change at 4 wk	2.1 ± 0.6	0.8 ± 0.5						

↑ Increase indicates an improvement; —, data not collected.

[*] *P* value for treatment difference is ≤.01.

[†] *P* value ≤.10.

[‡] *N* = 367 and N = 95 for adults and children at 16 wk, respectively.

[§] Number of patients with follow-up data on well-being measures.