Interim Analysis: The Effect of Adrenocorticotropin Gel (HP Acthar Gel) In Combination with Methotrexate in Newly Diagnosed Rheumatoid Arthritis Patients from a Clinical and Structural Perspective

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BACKGROUND

Although adrenocorticotropin (ACTH) gel was approved by the FDA for the treatment of rheumatoid arthritis (RA) in 1952, data on its clinical and structural benefits for the treatment of RA are limited. ACTH is composed of 39 amino acids, of which, the first 13 alone, form alpha-melanocyte stimulating hormone. By inhibiting cytokine action and inflammatory cell migration, ACTH has been effective in multiple inflammatory disorders in humans and adrenalectomized rats.[1] Emerging evidence related to the melanocortin system suggests that steroid-independent mechanisms of ACTH gel, in addition to steroidogenesis, may produce anti-inflammatory and immunomodulatory effects,[2] which can have a significant impact in the management of inflammatory disorders such as RA.

OBJECTIVES

The goal of this study was to evaluate the effects of ACTH gel on the widely accepted clinical and structural endpoints in patients with early RA. The purpose of this poster is to present the interim results.

METHODS

This was a 6-month, randomized, open-label, Phase II study. It consisted of three distinct study periods: a 1-month screening period, a 6-month study trial period, and a follow-up period of 6 months with visits at 1-, 3-, and 6-months after study completion. Fourteen men and women (>18 years of age) with early RA as defined by 2010 EULAR/ACR classification critieria,[3] received 15 mg methotrexate (MTX) weekly and 80 U ACTH gel weekly or biweekly. Baseline characteristics for each subject included a minimum of 6 tender and swollen joints, a Clinical Disease Activity Index (CDAI) score of >6.0 (with a mean score of 39.3) and presence of at least 1 of the following: osteitis, synovitis, or erosions on MRI (Esaote 0.3T) upon enrollment (Table 1). Concomitant nonsteroidal anti-inflammatory drug (NSAID) therapy was permitted however, disease modifying anti-rheumatic drugs (DMARDs) and corticosteroid use other than MTX, was prohibited.

RESULTS

We report results of 7 patients dosed weekly and 7 patients dosed biweekly with 80 U ACTH gel. In the biweekly-dosed group, all patients showed a clinical response, with an average of 84% improvement in CDAI score after 6 months (Table 2). Two patients in this group achieved remission, 3 achieved low disease activity, and 2 achieved medium disease activity. In the weekly-dosed group, 5 of 7 patients showed a clinical response, with a group average of 61.1% improvement in CDAI score after 6 months (Table 2). One patient remained at high disease activity and 1 patient terminated early due to lack of efficacy. Taking into consideration both groups, 12 of 14 patients showed a clinical response beginning at 3 months (71.2% CDAI improvement), which persisted through 6 months of treatment (71.0% CDAI improvement). Structural MRI findings varied between treatment groups. In the biweekly-dosed group, 5 patients showed regression in synovitis, while 2 patients showed regression in osteitis. In the weekly-dosed group, 3 patients showed regression in synovitis and 3 patients showed regression in osteitis. Overall, erosions were unchanged or regressed in 9 patients and progressed in 3 patients. Radiographic changes as seen in Figures 1 and 2, indicate resolution of erosion and osteitis. No significant adverse events were reported.

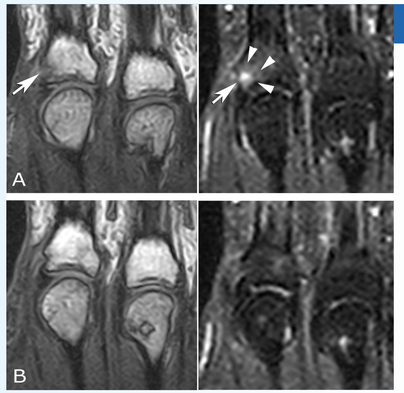

FIGURE 1

(A) Baseline T1-weighted (left) and STIR (right) MRI of the hand reveal a small erosion with a halo of moderate osteitis (arrowheads) involving the radial facet of the base of the second proximal phalanx (arrow).

(B) At 12 weeks, the erosion and osteitis have resolved.

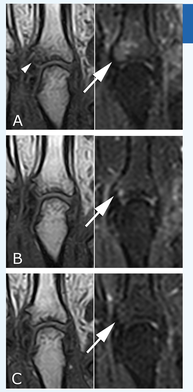

FIGURE 2

(A) Baseline T1-weighted (left) and STIR (right) MRI of the hand reveal subtle erosion (arrowhead) of the radial facet of the base of the third proximal phalanx with significant adjacent osteitis (arrow).

(B) At 12 weeks, the erosion has resolved and osteitis has regressed (arrowhead).

(C) At 24 weeks, osteitis has completely resolved (arrow).

TABLE 1

Patient Demographics	
Females	**12**
Black	6
White	3
Hispanic	3
Males	**2**
White	1
Black	1

TABLE 2

	Patient	CDAI			Disease Activity	% Improvement at 6 months
		Baseline	3 months	6 months		
Once Weekly	1	25.3	2.7	19.6	MDA	22.5
	2	35.8	16.7	9.5	LDA	73.5
	3	49.5	ET	ET	ET	ET
	4	36.6	12.6	9.3	LDA	74.6
	5	48.3	18.8	41.4	HDA	14.3
	6	49.8	18.3	5.5	LDA	89.0
	7	19.0	1.0	2.9	LDA	84.7
Average		37.8	11.7†	14.7†		59.8†
	Patient	CDAI			Disease Activity	% Improvement at 6 months
		Baseline	3 months	6 months		
Twice Weekly	1	34.4	5.1	15.9	MDA	53.8
	2	55.9	7.2	5.4	LDA	90.3
	3	37.7	14.1	0.7	Rem	98.1
	4	44.8	0.8	0	Rem	100
	5	42.2	5.3	12.1	MDA	71.3
	6	45.9	15.0	4.4	LDA	90.4
	7	24.8	25.4	7.2	LDA	71.0
Average		40.8	10.4	6.5		82.1
Total Average*		39.3	11.0	10.6		71.0

*Average of once weekly and twice weekly dosing.
†Average of 6 patients as 1 patient terminated the study early.
Early Termination (ET); Low Disease Activity (LDA) [2.9 – 10.0]; Moderate Disease Activity (MDA) [10.1 – 22.0]; High Disease Activity (HAD) [>22.1]; Remission (Rem) [≤2.8]

CONCLUSION

- The results of this interim analysis suggest a clinical and structural benefit with the use of ACTH gel in combination with MTX in early RA
- This combination therapy proved to be safe in this patient population
- It appears that the biweekly-dosed group obtained a more robust clinical and structural response; at 6 months, this group showed an improved, sustained outcome
- These data suggest that use of ACTH gel may result in a very effective treatment combination with MTX for early RA, possibly reducing the need for step-up biologic therapy over time
- The varying effects of ACTH gel on the melanocortin system justifies additional exploration of its use in other RA cases
- Further research is needed to determine if these results can be maintained on MTX therapy alone after discontinuation of ACTH gel

DISCUSSION

- Because ACTH is a melanocortin peptide, it is able to induce a small, steroid-dependent effect and a broader steroid-independent, anti-inflammatory effect[2]
- It carries its effects through interacting with MC1R-MC5R receptors[1], which inhibit pro-inflammatory signals and induce cytoprotective and anti-inflammatory signals[4]
- The structural benefits and anti-inflammatory effects of ACTH were demonstrated in the radiographs and clinical endpoints analyzed

Reference

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