Toreforant, A Histamine H4 Receptor Antagonist, in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: Results of 2 Phase II Studies

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ABSTRACT. ***Objective.*** To assess toreforant (selective histamine H_4 receptor antagonist) in active rheumatoid arthritis (RA).

Methods. In a phase IIa, double-blind, placebo-controlled test, 86 patients were randomized (2:1) to once-daily toreforant 100 mg or placebo for 12 weeks. In phase IIb, double-blind, placebo-controlled, dose-range–finding evaluations, 272 patients were randomized (1:1:1:1) to once-daily placebo or toreforant 3/10/30 mg. Primary efficacy endpoints for both studies were Week 12 changes in 28-joint Disease Activity Score–C-reactive protein (DAS28-CRP).

Results. Phase IIa testing was terminated prematurely (patient fatality; secondary hemophagocytic lymphohistiocytosis). Posthoc analyses indicated toreforant 100 mg/day reduced RA signs/symptoms through Week 12. Phase IIb testing, however, showed no significant Week 12 improvement in DAS28-CRP with toreforant.

Conclusion. Toreforant was not effective in phase IIb testing. (J Rheumatol First Release July 15 2016; doi:10.3899/jrheum.160164)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune inflammatory disorder[1]. Failure to achieve/maintain adequate response and/or intolerance to existing therapies yields a need for additional agents, including novel oral agents, to expand availability of effective RA treatments.

The histamine H_4 receptor (H_4R)[2,3] is expressed on many hematopoietic cells as well as human synovial cells from patients with RA[4,5,6,7]. H_4R inhibition reduces cytokine release and migration from many cells including mast cells and dendritic cells. Because mast cells are highly activated in RA[8] and their presence is a prerequisite in some arthritis models[9], such inhibition may ameliorate RA signs/symptoms. Further, dendritic cells activate antigen-presenting cells and T cells; thus, their inhibition may interfere with RA propagation. H_4R-deficient or H_4R-antagonist–treated mice were protected in several arthritis models[10,11].

Toreforant (JNJ-38518168; CAS Registry Number 952494-46-1) is a novel, orally active, selective H_4R antagonist. Following initial testing in healthy volunteers, toreforant trials were undertaken in patients with active RA despite methotrexate (MTX) therapy in phase IIa (safety, tolerability, and efficacy; ClinicalTrials.gov Identifier NCT00941707; EudraCT Number 2009-012118-27), followed by phase IIb (dose-ranging efficacy and safety; ClinicalTrials.gov Identifier NCT01679951; EudraCT Number 2011-002840-29) trials. The results are summarized herein.

MATERIALS AND METHODS

Phase IIa trial. This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with active RA despite MTX therapy. About 90 patients were to be randomized (2:1) to toreforant 100 mg or matching placebo capsules given once daily for 12 weeks.

Phase IIb trial. Phase IIb trial participants were adults with RA for ≥ 6 months who had received MTX for ≥ 6 months, with a stable dose for ≥ 8 weeks. Patients (n = 272) were randomly (1:1:1:1) assigned to receive toreforant 3, 10, or 30 mg/day or placebo once daily for 24 weeks. Phase IIa/IIb trial methodologies are described in the Supplementary material, available at jrheum.org.

RESULTS

Phase IIa trial. The toreforant phase IIa trial was conducted from December 2009 to November 2010 at 26 sites in 9 countries. The toreforant phase IIa trial was terminated prematurely because of a fatal serious adverse event (SAE). The patient's rapid deterioration, her fatal outcome, and the initially unclear cause/relationship of her death to the study drug led to immediate termination of the study by the sponsor. Subsequently, an extensive investigation of the cause of death and the possible relationship to toreforant and the H_4R target was pursued and included consultation with external subject matter clinical experts. Based on this review, the most likely cause of death was determined to be secondary hemophagocytic lymphohistiocytosis (sHLH), a rare immune activation syndrome that usually occurs in individuals with autoimmune disease. The causal relationship between toreforant and sHLH was considered unlikely, but cannot be ruled out entirely, taking into account the pathogenesis of sHLH, the known effects of H_4R antagonism, and the preclinical toxicological profile of toreforant.

At the time of early termination, 86 patients had been enrolled, 36 had completed the study, and 86 were included in the safety and intent-to-treat populations for analyses. All 86 randomized patients (58 toreforant, 28 placebo) received ≥ 1 dose of the assigned study agent. Supplementary Tables 1 and 2, available at jrheum.org, give summaries and descriptions of patient disposition and baseline patient characteristics, respectively. Baseline patient/disease characteristics were generally consistent between the treatment groups (Supplementary Table 2). At steady state (weeks 2–8), the average toreforant trough concentration was about 385 ng/ml (study termination precluded Week 12 pharmacokinetic data analysis).

Post-hoc efficacy analyses indicated toreforant 100 mg/day through 12 weeks reduced RA signs/symptoms based on improvements in 28-joint Disease Activity Scores incorporating C-reactive protein (DAS28-CRP; Figure 1A) and American College of Rheumatology ≥ 20% improvement (ACR20) responses (Figure 1C). The baseline-adjusted analysis of covariance of change in DAS28-CRP showed statistically significant treatment benefits from weeks 2–12. The adjusted mean treatment difference [least square (LS) mean; toreforant minus placebo] at Week 12 was –0.853, which was statistically significant ($p = 0.037$) despite small sample sizes (31 vs 14, respectively). Higher proportions of toreforant-treated than placebo-treated patients achieved ACR20 responses from weeks 1–12, and Cochran-Mantel-Haenszel (CMH) analysis indicated significant treatment differences at weeks 2/4/12 (Figure 1C). Trends of improvement were observed in each ACR component, including CRP (Supplementary Figure 1A, available at jrheum.org). Higher proportions of toreforant-treated than placebo-treated patients achieved Health Assessment Questionnaire–Disability Index (HAQ-DI) response (improvement ≥ 0.30) from weeks 1–12, and CMH analysis showed statistically significant treatment differences at weeks 1/2/4/8 (Supplementary Figure 2A, available at jrheum.org).

Overall, 50% of placebo-treated and 59% of toreforant-treated patients reported treatment-emergent AE. The most common AE included arthralgia, back pain, RA (possibly because of flare or worsening), nasopharyngitis, and nausea. Six patients (10%) in the toreforant group and 1 (4%) in the placebo group experienced SAE (Table 1). As mentioned, 1 SAE was sHLH that had a fatal outcome. The other SAE reported in the toreforant 100-mg/day group included RA, arthralgia, yersinia infection, and spinal compression fracture. Most abnormal chemistry/hematology values were mild to moderate in intensity; measurements of toxicity grades > 2 were transient and not clinically significant. Reversible, modest increases in creatinine levels were observed in the toreforant group.

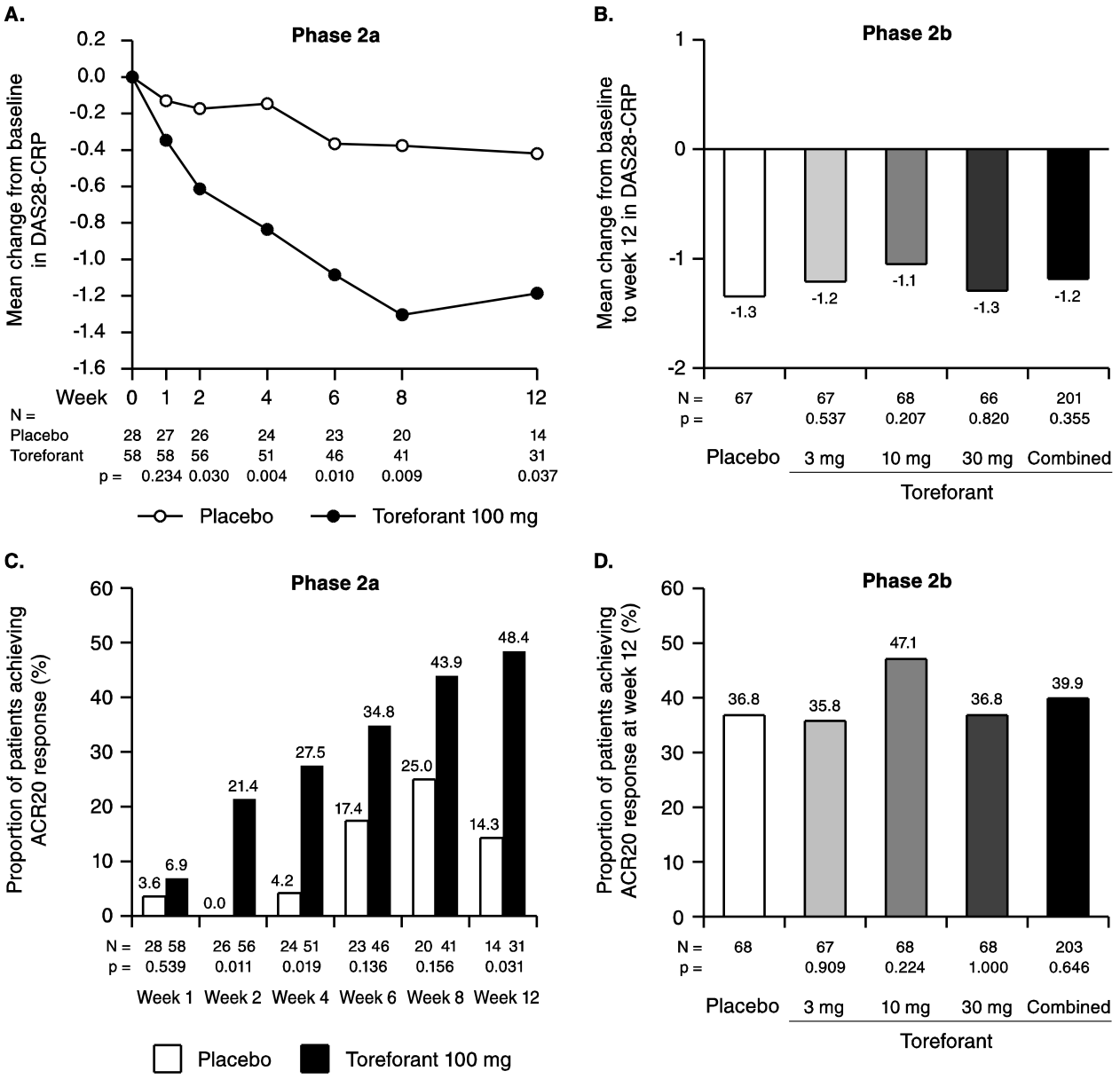

Figure 1. Mean changes from baseline in DAS28-CRP over time in the phase IIa (A) and phase IIb (B) studies, and the proportions of patients achieving ACR20 response over time in the phase IIa (C) and phase IIb (D) studies. Phase IIa analyses used observed cases on treatment with LOCF of last visit before treatment failure, and phase IIb analyses used the mITT study population. ACR20: American College of Rheumatology ≥ 20% improvement; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; LOCF: last observation carried forward; mITT: modified intent-to-treat.

Phase IIb trial. The toreforant phase IIb trial was conducted at 78 sites from October 31, 2012 to July 3, 2014 in 15 countries. Among 272 randomized patients, 55 (20%) discontinued the study agent, most commonly because of AE (7%), sponsor termination of study (6%), lack of efficacy (5%), and for reasons classified as "other" (7%; Supplementary Table 1, available at jrheum.org). Baseline clinical disease characteristics were generally well balanced across the treatment groups, with the exception of apparent longer disease duration among toreforant than placebo groups (Supplementary Table 2, available at jrheum.org).

Compared with placebo, no improvement in DAS28-CRP was observed with toreforant at Week 12 (study primary endpoint) or Week 24; there also was no indication of dose response (Figure 1B, Supplementary Figure 2B). No treatment effect was observed for ACR20 response (Figure 1D, Supplementary Figure 2C), CRP levels (Supplementary Figure 1B), change in HAQ-DI score (Supplementary Figures 2D, 2E), or other secondary efficacy measures (see Supplementary material, available at jrheum.org) at weeks 12 or 24. Subgroup analyses at Week 12, based on LS mean differences and 95% CI, showed no treatment benefit of any

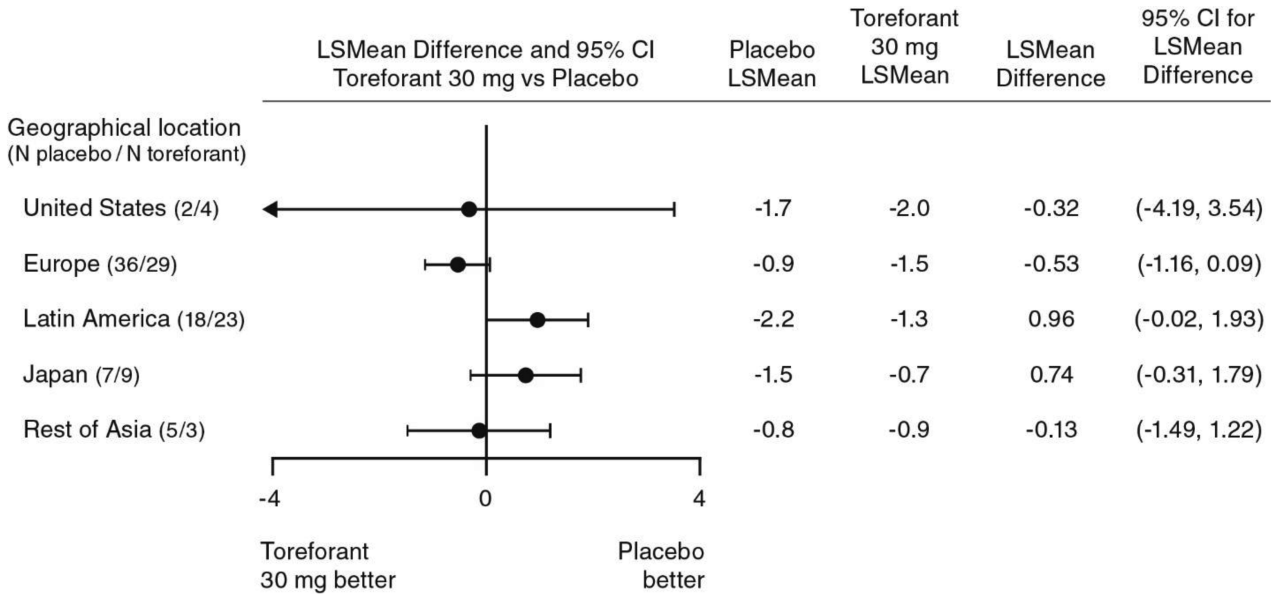

Figure 2. Treatment group differences in changes in DAS28-CRP from baseline to Week 12 by geographic region in the phase IIb study. DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; LS mean: least square mean.

Table 1. Summary of adverse events for the phase IIa and phase IIb trials. Data are n (%) unless otherwise indicated.

	Phase IIa		Phase IIb	Phase IIb Toreforant			
	Placebo	Toreforant, 100 mg	Placebo	3 mg	10 mg	30 mg	Combined, 30 mg*
Safety population, n	28	58	68	67	68	68	87
Patients with AE	14 (50)	34 (59)	45 (66.2)	39 (58.2)	42 (61.8)	40 (58.8)	46 (52.9)
Common AE (≥ 5% of patients)							
Nasopharyngitis	1 (4)	3 (5)	7 (10.3)	2 (3.0)	5 (7.4)	8 (11.8)	8 (9.2)
Urinary tract infection	—	—	2 (2.9)	4 (6.0)	4 (5.9)	5 (7.4)	5 (5.7)
Bronchitis	—	—	2 (2.9)	4 (6.0)	3 (4.4)	4 (5.9)	4 (4.6)
Diarrhea	—	—	1 (1.5)	2 (3.0)	1 (1.5)	8 (11.8)	8 (9.2)
Arthralgia	1 (4)	6 (10)	—	—	—	—	—
Back pain	0	4 (7)	—	—	—	—	—
RA, possible flare/worsening	1 (4)	3 (5)	—	—	—	—	—
Nausea	0	3 (5)	—	—	—	—	—
Patients who died	0	1 (2)	0	0	0	0	0
Patients with SAE	1 (4)	6 (10)	5 (7.4)	3 (4.5)	5 (7.4)	2 (2.9)	2 (2.3)
SAE occurring in > 1 patient	1 (4)	2 (3)	—	—	—	—	—
AE affecting dosing in phase IIa**/leading to study agent discontinuation in phase IIb	4 (14)	6 (10)	5 (7.4)	6 (9.0)	3 (4.4)	3 (4.4)	3 (3.4)
AE occurring in ≥ 1 patient	—	—	1 (1.5)	2 (3.0)	1 (1.5)	0	0

* Includes 19 patients who early escaped from placebo, 3 mg, or 10 mg to receive 30 mg at Week 16. **All AE affecting dosing in the phase IIa study each occurred in 1 single patient only. AE: adverse event; SAE: serious AE; RA: rheumatoid arthritis.

toreforant dose versus placebo for DAS28-CRP changes, although numerically greater improvement was observed with toreforant 30 mg versus placebo among European patients (Figure 2). Notably, placebo response assessed by LS mean (95% CI) in DAS28-CRP change varied across geographic regions, with the lowest improvement in Europe (–0.9; ~53% of placebo patients) and the highest in Latin America (–2.2; ~26% of placebo patients; Figure 2) at Week 12.

The mean steady-state plasma maximum exposures following toreforant 3/10/30 mg/day were 11.5/46.4/195 ng/ml, respectively. The respective mean trough concentrations (Cmin) were 7.02/26.9/104 ng/ml.

Through Week 28, the proportions of patients with ≥ 1 AE were comparable between toreforant (59%) and placebo (66%) groups (Table 1). Several common (≥ 5%) AE in the combined toreforant group as derived from Table 1, i.e.,

urinary tract infection (6.3%), bronchitis (5.3%), and diarrhea (5.3%), appeared more prevalent versus placebo (2.9%, 2.9%, and 1.5%, respectively). A dose response in the overall occurrence of AE across the toreforant 3 mg (58%), 10 mg (62%), and combined 30 mg (53%) groups was not observed (Table 1), and no dose-related trends were seen in individual AE, with the exception of diarrhea (combined toreforant 30-mg/day group 9.2% vs placebo 1.5%). Most diarrhea cases were mild, self-limiting, and of short duration.

Through Week 28, 7% and 5% of placebo- and combined toreforant-treated patients, respectively, had ≥ 1 SAE (Table 1). All SAE were singular events, and no specific pattern of association between SAE and active treatments was identified. Two serious infections were reported: gastroenteritis (toreforant 10 mg) and postoperative wound infection (toreforant 3 mg). No death, opportunistic infection, tuberculosis, sHLH, or malignancy was reported. Similar proportions of placebo-treated (7%) and combined toreforant-treated patients (6%) discontinued the study agent as a result of an AE (Table 1).

A small and reversible mean increase from baseline in serum creatinine level was observed in the combined toreforant 30-mg (but not 3- or 10-mg) group versus placebo. No consistent, clinically meaningful, and/or treatment-related changes were observed in other laboratory variables, vital signs, or electrocardiogram measures, including corrected QT interval.

DISCUSSION

The initial efficacy, albeit modest, and safety results with toreforant 100 mg/day in the phase IIa study were considered supportive of further study in RA. However, a subsequent phase IIb dose-range finding study in a similar patient population did not meet its primary/secondary endpoints.

There are several possible explanations for the interstudy difference in results. Efficacy analyses from the phase IIa study were posthoc and based on limited datasets and therefore could have yielded the wrong conclusion. It also is possible that the placebo response was underestimated because of the small sample size. Alternatively, the phase IIa dose was 100 mg/day, whereas lower doses were studied in phase IIb to maximize the safety. Based on the levels needed for efficacy in preclinical mouse arthritis models, all doses studied (3, 10, 30, and 100 mg) should have been at the top of the dose-response curve and yielded comparable efficacy based on the mean Cmin values being above 6 ng/ml. However, using preclinical models for dose prediction in humans can be unreliable and it is possible that toreforant is efficacious at 100 mg/day but not 30 mg/day.

An additional explanation is that the high placebo response in phase IIb testing may have masked efficacy. Phase IIb ACR20 placebo response rates were 37% and 50% at weeks 12 and 24, respectively (vs phase IIa Week 12 ACR20 placebo response rate of 14%). Placebo response rates varied between geographic regions in the phase IIb study, with Latin American countries having a high placebo response (LS mean of DAS28-CRP change from baseline: –2.2) and European countries having the lowest response (LS mean of DAS28-CRP change from baseline: –0.9) at Week 12. While interstudy comparisons are difficult, it is notable that toreforant efficacy appeared consistent between the phase IIa study (LS mean difference in DAS28-CRP change from baseline for toreforant 100 mg/day vs placebo: –0.85) and the phase IIb European sites (toreforant 30 mg/day vs placebo: –0.53) after 12 weeks of treatment.

One patient died 21 days after starting toreforant 100 mg/day in the phase IIa trial. Following intensive review, the most likely cause of death was considered to be sHLH. Based on sHLH pathogenesis, it is unlikely that this death was related to toreforant or H_4R antagonism, but a causal relationship between the compound and the SAE cannot be completely ruled out. No sHLH reports occurred in the larger phase IIb study of longer duration that assessed toreforant 3/10/30 mg/day.

In the phase IIa study with toreforant 100 mg/day, 50% of placebo-treated and 59% of toreforant-treated patients reported AE. Similar AE rates were observed in the phase IIb study (66% placebo, 59% combined toreforant). All SAE in both studies were singular events, and no specific pattern of association between SAE and active treatments was identified. Two serious infections (gastroenteritis 10 mg, postoperative wound infection 3 mg), but no deaths, opportunistic infection, tuberculosis, or malignancy, were reported. For both studies, no consistent, clinically meaningful changes from baseline in vital signs, electrocardiogram results, or laboratory variables were observed, with the exception of a small, reversible mean increase in the serum creatinine level in the toreforant 100-mg and 30-mg groups that is consistent with toreforant being a reversible inhibitor of human organic cation transporter 2 and with effects seen with other such agents[12].

Thus, while some improvement in RA signs/symptoms through Week 12 was observed in the phase IIa study, no efficacy was observed with toreforant at lower doses in a subsequent phase IIb study. The discordant finding may suggest that toreforant is only efficacious at higher doses or that sample size and posthoc analysis of the phase IIa study led to overestimation of efficacy.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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