RESULTS OF A PHASE 2 STUDY OF RG6125, AN ANTI-CADHERIN-11 MONOClonAL ANTIBODY, IN RHEUMATOID ARTHRITIS PATIENTS WITH AN INADEQUATE RESPONSE TO ANTI-TNFALPHA THERAPY

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Background: Cadherin-11 is expressed on fibroblasts in joints of RA patients and augments fibroblast-mediated inflammation, pannus formation and tissue invasion (1). RG6125 is a novel humanized monoclonal antibody directed against Cadherin-11.

Objectives: To assess the safety, tolerability and efficacy of RG6125 as adjunctive treatment in patients with moderately to severely active RA and an inadequate response to anti-TNFα therapy.

Methods: The Phase 2 study was conducted as a multicenter, randomized, double-blind, placebo-controlled study. Patients were randomly assigned (2:1) to receive 810 mg of RG6125 or placebo by IV infusion. In the treatment period, patients received RG6125 or placebo IV infusions twice every two weeks and then monthly for a total of 4 dose administrations up to Week 12. The primary efficacy endpoint was the proportion of patients with ACR50 response at Week 12.

Results: Demographics: 109 patients were randomized (98 female) to either placebo or RG6125. Safety: 8 (11.1%) of 12 patients experienced serious adverse events (SAEs). Serious SAEs were reported in 10 patients (92.3%). Non-Serious SAEs were reported in 9 patients (81.8%). Safety: No cases of death were reported during the study. Safety: There were no significant safety differences between groups.

Efficacy: At baseline, the mean (SD) Clinical Disease Activity Index (CDAI) was 307 (81). At Week 12, the mean (SD) CDAI was 290 (80). Safety: The most common adverse events were gastrointestinal adverse events (12.9% vs. 8.1%) were noted on RG6125 compared to placebo, respectively. There were no significant safety differences between groups.

PK/PD: Pharmacokinetics of RG6125 appears linear at the dose range tested. No significant differences were observed in PK parameters between groups. No significant differences were observed in PD parameters between groups.

Conclusion: RG6125 was well tolerated with only mild to moderate AEs. RG6125 did not show a discernible treatment effect in RA patients in combination with anti-TNFα-blocers over placebo.

REFERENCE:

Disclosure of Interests: Rebecca Finch Shareholder of: Roche, Employee of: Roche, Alexandre Sostelly Shareholder of: Roche, Employee of: Roche, Kim Sue-Ling Shareholder of: Roche, Employee of: Roche, Angela Blaeuer Shareholder of: Roche, Employee of: Roche, Guillelmette Duchateau-Nguyen Shareholder of: Roche, Employee of: Roche, Lidaia Ukarma Shareholder of: Roche, Employee of: Roche, Claire Petry Shareholder of: Roche, Employee of: Roche, Patanjali Ravva Shareholder of: Roche, Employee of: Roche, Peter Villiger: None declared, Uwe Junker Shareholder of: Roche, Employee of: Roche


SERIOUS INFECTIONS IN OFFSPRING EXPOSED IN UTERO TO NON-TNF BIOLOGICS AND TOFACITINIB

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Background: During pregnancy, maternal circulating immunoglobulins G (IgG) are actively transported across the placenta through their Fc portion. Thus, TNFi and other biologics harbouring an Fc part have the potential to transfer across the placenta, often reaching higher fetal than maternal levels.[1] In addition, it is postulated that small-molecule drugs may cross the placenta, although this remains unconfirmed. As fetuses could be exposed to therapeutic (or potentially supra-therapeutic) levels of biologics and small molecules, there are concerns that these agents could cause immunosuppression in exposed offspring.

Objectives: We compared the risk of serious infections in children born to mothers with chronic inflammatory diseases who used non-TNF biologics or tofacitinib during pregnancy, versus unexposed offspring and children exposed to TNFi in utero.

Methods: We identified all women with ≥1 hospitalization for delivery after a diagnosis of rheumatoid arthritis (RA), anklyosing spondylitis (AS), psoriasis (PsO), psoriatic arthritis (PsA), or inflammatory bowel diseases (IBD), and a randomly selected group of unaffected mothers, matched 4:1 for age, year of delivery, and state of residence, using MarketScan data (2011-2016). Only women continuously enrolled within MarketScan for ≥12 months prior to delivery and with available child linkage were included. We defined tofacitinib, TNFi and non-TNF biologic (i.e. abatacept, rituximab, tocilizumab, ustekinumab, vedolizumab) exposure based on ≥1 filled prescription and/or infusion procedure code during pregnancy and/or the preconception period. We ascertained serious infections in the offspring based on ≥1 hospitalization with infection as a primary diagnosis, within the first year of life. We also characterized all exposure groups according to maternal demographics, disease type, co-morbidities, pregnancy complications, and drug use (i.e. corticosteroids, DMARDs, biologics).

Results: We identified 16,490 offspring of mothers with RA (4,142), AS (381), PsO/PsA (5,743), and IBD (6,731), as well as 164,553 children born to unaffected mothers. We observed 2 cases of serious infections in children exposed to tofacitinib or non-TNF biologics (tocilizumab 4, abatacept 34, rituximab 6, tocilizumab 12, ustekinumab 42) and 1,611 to TNFi during pregnancy.

Conclusion: In the largest cohort of inflammatory disease offspring ever assembled, we detected very few serious infections in children exposed to non-TNF biologics or tofacitinib. More studies are necessary to precisely determine the specific effects of individual non-TNF biologic and small-molecule drugs on the risk of serious infections in exposed offspring.

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