IA-14069, A NOVEL SMALL-MOLECULE INHIBITOR DIRECT-TARGETING TUMOR NECROSIS FACTOR-α (TNF-α), ATTENUATES COLLAGEN INDUCED ARTHRITIS

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Background: Rheumatoid arthritis (RA) is systemic autoimmune disease that is characterized by autoreactive immune cells and various cytokine-mediated inflammation in multiple joints, leading to cartilage degradation, bone erosion and finally irreversible joint destruction1. The inflammatory cytokine tumor necrosis factor-α (TNF-α) is known to play a central role in several chronic immune-mediated inflammatory disorders2.

Objective: Despite the great success of anti-TNF-α biological drugs in the treatment of RA, no chemical drug targeting TNF-α is available. Here we report that IA-14069, a novel small molecule inhibitor, binds directly to TNF-α and inhibits TNF-α activities both in vitro and in vivo.

Methods: IA-14069 was screened and identified by competitive binding assay using TNF-α and TNF receptor. In vitro neutralization activity of IA-14069 against TNF-α was determined using MTT assay. The direct binding of IA-14069 to TNF-α was demonstrated by surface plasmon resonance and bead pull-down assays. The inhibition of TNF-α-TNF receptor interactions by direct binding of IA-14069 to TNF-α was analyzed by flow cytometry. Levels of phosphorylated ikBα (p-IkBα) and NF-kB p65 were analyzed by western blot. IA-14069 was orally administered to TNF-α transgenic (TNF-α-TG) RA mice at 3.3 or 33 mg/kg twice per week or at 25, 50 or 100 mg/kg 3 times per week for preventive or therapeutic effect, respectively. In vivo therapeutic efficacy of IA-14069 or methotrexate was evaluated in collagen-induced arthritis (CIA) mice immunized with bovine type II collagen (CII) emulsified in complete Freund’s adjuvant.

Results: IA-14069 potently inhibits both TNF-α-induced cytotoxicity (IC50 < 0.7 μM) which directly binds to TNF-α and TNF-α-triggered signaling (p-IkBα and NF-kB p65) activities. The therapeutic as well as preventive anti-RA effects of IA-14069 were demonstrated in TNF-α-TG and CIA models. IA-14069 and MTX had synergistic effects in the CIA therapeutic model. According to pharmacokinetic analysis, IA-14069 showed significant bioavailability. In addition, no in vivo toxicity was observed even under treatment of excessive amount of IA-14069.

Conclusion: The data indicate that IA-14069 can be a novel and potent TNF-α inhibitor for the treatment of RA and other inflammatory diseases.

EFFECTIVENESS ANALYSIS FOR SPANISH PATIENTS

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Background: Lesinurad, a medication that inhibits uric acid reabsorption, has been recently approved in combination for the treatment of patients with gout who do not reach therapeutic serum urate target with xanthine-oxidase inhibitors monotherapy.

Objectives: To assess the incremental cost-effectiveness ratio of adding lesinurad to allopurinol as 2nd line therapy, compared to febuxostat for the management of patients with gout in Spain.

Methods: A Markov model comprising 6 health-states representing the disease evolution was used to estimate in 6-months cycles, the lifetime accumulated cost and benefits in terms of quality-adjusted-life-year (QALY) in an hypothetical cohort of patients stratified according to serum uric acid levels observed on pooled CLEAR trials: 18.3% (>6 mg/dL), 63.7% (6-8 mg/dL), 15.2% (8-10 mg/dL) and 2.3% (>10 mg/dL). During the simulation, patients could either continue with 2nd line treatment with lesinurad (200mg/daily) plus allopurinol (400mg/daily) or febuxostat (80mg/daily), switch to allopurinol monotherapy (271mg/daily) in case of intolerance or discontinue treatment. Proportion of topheaceous gout (18.9%) was considered at each health-state. The efficacy of treatments was captured in the transition probabilities between health states which were derived from findings on CLEAR 1, CLEAR 2 and EXCEL clinical trials. Quality of life related to gout severity (topheaceous or non-topheaceous) and flare frequency was considered by means of utilities estimated from SF-36 scores of the pooled CLEAR trials which were mapped to EQ-5D values. The total cost estimation (€, 2018) included drug acquisition cost (retail prices with mandatory deduction applied), disease monitoring (£377.03 for first 6-month period, €329.95/ subsequente year) and flare management (€301.69). Unitary costs derived from local cost databases and literature. A 3% annual discount rate was applied for cost and outcomes. Sensitivity analyses (SA) were carried out.

Results: Lesinurad added to allopurinol provided higher QALYs (14.79) than febuxostat (14.69). Total accrued cost per patient were lower (€4,819.13) with lesinurad and allopurinol (€4,659.27) compared to febuxostat (€5,478.40). Lesinurad plus allopurinol resulted a dominant option (more effective and less costly) compared to febuxostat. SA results confirmed the model robustness.

Conclusion: These results suggest that treatment with lesinurad 200 mg/day plus allopurinol 400 mg/day compared to febuxostat 80 mg/day is an effective second option for the management of hyperuricemia in patients with gout who did not reach therapeutic urate target to previous allopurinol monotherapy, associated to cost-savings for the Spanish National Health System.

REFERENCES:

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