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Active Immunization With TNF-Kinoid In Rheumatoid Arthritis Patients With Secondary Resistance To Tumor Necrosis Factor-Alpha Antagonists Is Safe And Immunogenic.

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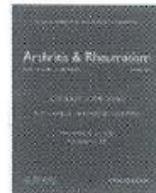
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Background/Purpose:

Blocking TNF alpha (TNF α) with monoclonal antibodies (mAbs) has been successful in the treatment of rheumatoid arthritis. However secondary resistances are frequent and impose treatment changes. Active immunization with a TNF-Kinoid that safely induces self polyclonal anti-TNF α antibodies (Abs) could be an alternative to anti-TNF α mAbs. We evaluated the immunogenicity and safety of TNF-K in patients with rheumatoid arthritis and secondary resistance to TNF blockers.

Methods:

TNF α -Kinoid (TNF-K, Neovacs SA, Paris, France) is an immunotherapeutic composed of recombinant human TNF α conjugated to KLH, inactivated and adjuvanted with ISA-51 emulsion. 40 patients with active rheumatoid arthritis (DAS28 \geq 3.2) with history of positive clinical response to at least one TNF-blocker followed by secondary failure (35% IFX, 30% ADA, 42.5% ETA) were enrolled in a double-blind, placebo-controlled, phase 2 study to evaluate three different intramuscular doses of TNF-K (90, 180, 360 mcg) and two immunization schedules (D0 and 28 or D0, 7 and 28). Humoral immune responses were evaluated through titration of anti-TNF α

[Meeting Menu](#)[2012 ACR/ARHP](#)[Meeting Authors](#)[Meeting Abstracts](#)

and anti-KLH Abs and neutralization assay. The T cell response was assessed by lymphoproliferative assay with tritiated thymidine incorporation. Clinical response was evaluated by the ACR and EULAR core set response.

Results:

No related serious adverse event has been reported. Few minor transient local and systemic reactions have been recorded following immunization. Anti-TNF α Abs were induced in 50%, 75% and 91% of patients at 90 mcg, 180 mcg and 360 mcg, respectively. 100% of patients with three injections of 180 or 360 mcg had immunogenic response against TNF versus 67% in the groups receiving two injections. The anti-TNF antibody geometric mean titres were higher in patients who received 3 injections of 360 mcg. No lymphoproliferative response could be measured after stimulation with native TNF. Among the 21 patients who developed anti-TNF Abs, 48% present a moderate to good response according to EULAR score as opposed to only 31% of the 16 patients without Abs. A mean decrease of -14% of the C reactive protein level is measured in patients with Abs while in patients without Abs, the mean CRP level increased by 5%.

Conclusion:

Active immunization with TNF α kinoid to induce a polyclonal, self-anti-TNF α antibody response is safe and immunogenic. A clear dose-response was observed for the dose of kinoid as well as for the number of administrations. Association of anti-TNF Abs induced by the kinoid with clinical and biological responses were observed in patients included in this preliminary phase 2 study. Further studies are needed to confirm this new approach in RA.

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