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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. Patrick Durez[1], Pedro Miranda[2], Antoaneta Toncheva[3], Alberto Berman Sr.[4], Oscar L. Rillo[5], Yves Boutsen[6], Tatjana Kehler[7], Eugenia Mociran[8], LiAn Soto Saez[9], Bruno Fautrel[10], Xavier Mariette[11], Panayot Solakov[12], Eleonora Lucero[13], Tonko Vlak[14], Simeon Grazio[15], Ksenija Mastrovic[16], Rodica Chiriac[17], Géraldine Grouard-Vogel[18], Olivier Dhellin[18], Stéphane Ouary[18], Pierre Vandepapeliere[18] and Marie-Christophe Boissier[19]. [1]Université Catholique de Louvain, Brussels, Belgium, [2]Centro de Estudios Reumatologicos, Santiago de Chile, Chile, [3]National Multiprofile Transport Hospital, Sofia, Bulgaria, [4]Hospital Padilla, Tucuman, Argentina, [5]Hospital Tornú, Buenos Aires, Argentina, [6]UCL Mont-Godinne, Godinne, Belgium, [7]Thalassotherapia Opatija, Opatija, Croatia, [8]Emergency County Hospital Dr Constantin Opis, Maramures, Romania, [9]Sociedad Medica del Aparato Locomotor SA, Santiago de Chile, Chile, [10]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [11]Université Paris-Sud, Le Kremlin Bicetre, France, [12]Diagnostic and Consulting Center, Plovdiv, Bulgaria, [13]Centro Investigaciones Reumatológicas, Tucumán, Argentina, [14]University Hospital Split, Split, Croatia, [15]Clinical Hospital Center Sestre Milosrdnice, Zagreb, Croatia, [16]Clinical Hospital Sveti Duh, Zagreb, Croatia, [17]Rehabilitation clinical Hospital Iasi, Iasi, Romania, [18]NEOVACS SA, Paris, France, [19]Hopital Avicenne, Bobigny, France

Background/Purpose: Blocking TNF alpha (TNFα) 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-TNFα antibodies (Abs) could be an alternative to anti-TNFα mAbs. We evaluated the immunogenicity and safety of TNF-K in patients with rheumatoid arthritis and secondary resistance to TNF blockers.

Methods: TNFα-Kinoid (TNF-K, Neovacs SA, Paris, France) is an immunotherapeutic composed of recombinant human TNFα conjugated to KLH, inactivated and adjuvanted with ISA-51 emulsion. 40 patients with active rheumatoid arthritis (DAS28≥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-TNFα 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-TNFα 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 TNFα kinoid to induce a polyclonal, self-anti-TNFα 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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Etanercept Induces A Significant Decrease of Oxidative Stress and Osteoprotegerin Compared with Sdmard in Patients with Rheumatoid Arthritis. Claire I. Daien[1], Anne-Marie Dupuy Gorce[1], Edith Pinot[1], Thibault Mura[2], Jean-Paul Cristol[1], Bernard Combe[1] and Jacques Morel[1]. [1]Hopital Lapeyronie, Montpellier, France, [2]Hopital Gui De Chauliac, Montpellier, France

Background/Purpose: TNF-inhibitors are known to decrease cardiovascular events in rheumatoid arthritis (RA) as compared with synthetic disease modifying anti-rheumatic drugs (sDMARD). However, mechanisms involved remain to be explored. Osteoprotegerin (OPG) is increased and independently associated with coronary-artery atherosclerosis in patients with RA. Adiponectine has cardioprotective functions and joint-destruction role in RA. Oxidative stress, especially urinary F(2) isoprostanes, predicts cardiovascular mortality and is increased in RA. We aimed to explore metabolic parameters changes after 6 months of anti-TNF therapy or sDMARD in patients with RA.

Methods: Twenty-four patients were included in the etanercept (ETN) group and 17 in the sDMARD group. Metabolic parameters were evaluated at baseline and at 6 months. HOMA was calculated as (insulin*glycemia)/22.5. Urinary F(2) isoprostanes were assessed using negative ion chemical ionization gas chromatography-mass spectrometry. OPG and total adiponectine levels were determined by enzyme linked immunosorbent assay. Changes were evaluated using paired-t-tests or Wilcoxon matched-pairs signed rank tests and correlations using spearman tests.

Results: Patients of the ETN group had a significantly longer RA duration, were more often RF and ACPA positive and had more often erosions and steroids. Patients had similar blood pressure, body mass index (BMI), glycemic and lipid parameters, homocystein, OPG and isoprostanes at baseline in both groups. Adiponectine tended to be higher in ETN group (196 [126–228] vs 136 [196–286] μg/ml, p=0.08).

Isoprostanes at baseline correlated with triglycerides (r=0.42, p<0.05) and inversely correlated with HDL (r=−0.37, p<0.05), HbA1c (r=−0.38, p<0.05).OPG at baseline correlated with age (r=0.48, p<0.01), DAS28 (r=0.38, p<0.05), CRP (r=0.53, p<0.01), HbA1c (r=0.51, p<0.01).

A significant decrease of BMI at 6 months was observed in the ETN group (−0.6 ± 1.4 kg/m^2, p<0.05 and 1.8 ± 0.62 kg/m^2 in ETN and sDMARD group respectively). The BMI variation was significantly different between the 2 groups (p=0.02). No correlation was found between BMI change and steroid changes. No change in mean blood pressure, HOMA, HbA1c, cholesterol and homocystein was observed after 6 months of either treatment. A significant decrease of OPG (−0.93 ± 1.64 pmol/l, p=0.03 vs 0.35 ±2.05 pmol/l, NS; respectively in ETN and sDMARD groups), isoprostanes (−227 ± 243 pmol/mmol of urinary creatinine, p=0.01 vs −18± 141, NS) and a tendancy to adiponectine increase (62 ± 217 μg/ml, p=0.08 vs −13 ±67 μg/ml, NS) was found in patients treated with ETN at 6 months whereas no change was observed in the sDMARD group. Variations were different between the 2 groups for isoprostanes (p<0.05), with a tendancy for OPG (p=0.06) and adiponectine (p=0.09). Isoprostanes and OPG changes were not correlated with DAS28 or CRP variations between baseline and 6 months.

Conclusion: ETN induced a decrease of oxidative stress and OPG which may partially explain the protective cardiovascular effect of TNF inhibitors.

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Duration of Sustained Remission and Differences in Responce Between Medications, in Tumor Necrosis factor inhibitor Treated Rheumatoid Arthritis Patients. Jon T. Einarsson[1], Pierre Geborek[2], Tore Saxne[3] and Meliha C. Kapetanovic[4]. [1]Dept of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Sweden, Lund, Sweden, [2]Lund University, Lund, Sweden, [3]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [4]Dept of Clinical Sciences Lund, Lund, Sweden

Background/Purpose: Remission is increasingly becoming a treatment goal in rheumatoid arthritis (RA) patients and DAS28 remission criteria are widely used, despite their limitations.