BIOLOGICS AND RISK OF MALIGNANCIES: SCREENING PROCEDURES AND PATIENT FOLLOW UP

Dott. Fabrizio Cantini
U.O. Medicina II-Reumatologia
Ospedale di Prato

CURRENTLY EMPLOYED AND COMING UP BIOLOGICS

CURRENT

- ETANERCEPT
- INFLIXIMAB
- ADALIMUMAB
- RITUXIMAB
- ABATACEPT

COMING UP

- GOLIMUMAB
- TOCILIZUMAB
- OFATUMUMAB
- CERTOLIZUMAB
- DACLIZUMAB
- ....MUCH MORE

AVAILABLE DATA ON PATIENTS WITH RA,PsA,AS

- Anti-TNFα drugs data from RCTs, RCT open extension phases, US National Healthcare databases, National Registries (UK, Sweden)
- Anti-TNFα drugs data based on a larger number of patients and on a longer follow up period
- Rituximab and Abatacept data based on a lower number of patients recruited in RCTs

ANTI-TNFα DRUGS AND MALIGNANCIES

- TNFα exerts an important role in host defense and in the pathobiology of cancer through its action on natural killer cell- and CD8 lymphocyte-mediated killing of tumor cells
- An increase of malignancy occurrence has been considered as a possible adverse event of TNFα blockade

Balkwill F. Cytokine Growth Factor Rev 2002.
Mocellin S, et al. Cytokine Growth Factor Rev. 2005.

ANTI-TNFα DRUGS AND CANCER: EVIDENCE

- Data from Swedish register, and from one Japanese, one Canadian, and three US Healthcare databases: no increased frequency of all malignancies in patients receiving anti-TNFα agents compared to the general population and to those taking traditional DMARDs.

Schiff MH, et al. Ann Rheum Dis 2006; Setoguchi S, et al. Arthritis Rheum 2006; Kristensen LE et al. Ann Rheum Dis. 2007; Wolfe F et al. Arthritis Rheum. 2007; Geborek P, et al. Ann Rheum Dis. 2005 Takeuchi T, et al. Ann Rheum Dis 2007; Askling J, et al. Ann Rheum Dis 2008

ANTI-TNFα DRUGS AND MALIGNANCIES

A recent metanalysis of RCTs of infliximab and adalimumab reported a significantly higher occurrence of solid tumors in patients receiving the active drug compared to placebo

Bongartz T, et al. JAMA 2006

- **Askling J, Bongartz T. Malignancy and biologic therapy in rheumatoid arthritis.**
  Curr Opin Rheumatol 2008

Systematic review of RCTs of anti-TNFα drugs

- 36 RCTs of at least 12-week duration of IFX, ETN, and ADA to treat RA, PsA, and AS
- Recruited 12006 p.: 81 (0.67%) malignancies
- Active treatment 8015 p.= 60 (0.75%) malignancies
- Placebo 3991 p.= 21 (0.52) malignancies
- P: 0.15

Infliximab RCTs
7 RA, 2 PsA, 4 AS

- Recruited 3564 p.: 18 (0.50%)
- Study drug 2535 p.: 14 (0.55%) malignancies
- Placebo arm 1029 p.: 4 (0.39%) malignancies
- P: 0.71

Etanercept RCTs
9 RA, 2 PsA , 5 AS

- Recruited 4943 p.: 34 (0.68%) malignancies
- Study drug 3197 p.: 23 (0.72%) malignancies
- Placebo arm 1746 p.: 11 (0.63%) malignancies
- P: 0.71

Adalimumab RCTs
5 RA, 1 PsA, 1 AS

- Recruited 3499 p.: 30 (1.3%) malignancies
- Study drug 2283 p.: 24 (1%) malignancies
- Placebo arm 1216 p.: 6 (0.49%) malignancies
- P: 0.13

ABATACEPT RCTs
2 RA

- Recruited 2944 p.: 38 (1.29%) malignancies
- Study drug 1955 p.: 27 (1.38%) malignancies
- Placebo arm 989 p.: 11 (1.1%) malignancies
- P: 0.87

Rituximab RCTs
RA

- Trials in RA have so far not revealed any signal of increased short-term risk of cancer

Cohen SB, et al. Arthritis Rheum 2006

Anti-TNFα and malignancies (1)

- All but one malignancy occurred in RA
- Comparison between study drug and placebo arms for pre-existing risk factors for cancer?
- Combe's study (ETA/RA): 1 p. known to have MDS developed AML within 12 weeks from study entry
- Furst's trial (ADA/RA): 1 p. developed T-cell lymphoma 8 weeks after enrolment. Before study entry he had anorexia, weight loss, low-grade fever, and night sweats
- 8/60 (13.3%) cancers in study drug arms (7 breast and 1 endometrial) and 2/17 (11.8%) in placebo arms (2 breast) were estrogen-dependent

Anti-TNFα and malignancies (2)

- 14/60 (23.3 %) cancers in study drug and 6/21 (28.5%) in placebo arms were skin BCCs
- 21 (26.0%) of 81 malignancies occurred within 12 weeks from the enrolment.
- 16/60 (26.6%) were recorded in the active treatment and 5/21 (23.8%) in the placebo arms

Anti-TNFα and malignancies (3)

Long pre-clinic, asymptomatic phase of some solid cancers including lung, gastrointestinal, breast and genitourinary malignancies.

RCT DEFECTIVE CANCER SCREENING PROCEDURES ?

RCT cancer screening procedures

Current diagnosis of cancer or positive history of cancer over the previous 5-10 years, excluding basal cell carcinoma of the skin

PERSONAL CASE SERIES

ANTI-TNFα THERAPY AND MALIGNANCIES: IS THERE A NEED FOR MORE COMPREHENSIVE SCREENING PROCEDURES ?

C. Nannini, F. Cantini, L. Niccoli, C. Salvarani, I. Olivieri, EV. Lally. (Submitted)

Aim of the study

To evaluate the frequency of malignancies in patients with RA, PsA, and AS requiring anti-TNF selected with more comprehensive cancer screening procedures compared to patients screened with the RCT procedures.

Methods

STUDY PATIENTS

- Consecutive patients with active RA, PsA, and AS treated with anti-TNFα agents from January 2002 to December 2006 after the adoption of more comprehensive cancer screening procedures compared to those used in RCTs.

CONTROLS

- Consecutive patients with RA, PsA, and AS receiving the same drugs from 1999 to 2001 who were screened on the basis of diagnosis of cancer or positive history of cancer over the previous 10 years.

Outcome measure and follow-up

- Primary outcome measure was the frequency of cancer occurrence after starting therapy
- Patients were followed by the same rheumatologist with scheduled visits at baseline and every 4 months
- This interval was shortened in the case of urgent clinical problems
- All patients were instructed to call the centre in presence of worsening of previous arthritis, additional joint involvement, extra-articular manifestations, adverse events (AEs).

Statistical analysis

- Descriptive statistics and statistical differences were calculated using Microsoft Excel Software of Office Package for Windows XP, version 2003.
- Continuous variables were summarized by mean and standard deviation; categorical variables were displayed as number and percentage. T-test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables were used to calculate the differences between the study patients and controls.
- P values less than 0.05 were accepted as significant.

Cancer screening procedures

- **2002-2006. Study patients.** 363 consecutive patients underwent the following cancer screening procedures:

  -positive history or diagnosis of malignancy

  -abdominal ultrasound (US)

  -hormone replacement therapy cessation in postmenopausal women

  -In over 50s: chest radiograph and lung CT in heavy smokers; fecal occult blood detection; tumor markers determination.

- **Controls:** 73 patients treated between January 1999 and December 2001 screened with the RCT procedures.

CANCER SCREENING PROCEDURES

STUDY PATIENTS

ISTORY OF CANCER
IAGNOSIS OF CANCER
BDOMINAL ULTRASOUND
RT CESSATION IN PM WOMEN

CONTROLS

-HISTORY OF CANCER
-CURRENT DIAGNOSIS OF CANCER

OVER 50s
-HEAVY SMOKERS: LUNG CT
-OCCULT BLOOD IN THE STOOLS
-TUMOR MARKERS

Cancer screening procedures

- If any abnormality of 1 or more of these items patients were initially excluded from the treatment
- They underwent appropriate further clinical investigation
- If no malignancy was detected, patients started the therapy
- The same investigation was repeated at 12-month intervals
- The same screening procedures, with the exception of lung CT, were also repeated every 12 months in patients without any contraindication to treatment at first visit

RESULTS

- 36/363 (9.94%) study patients had at least 1 abnormal screening procedure
- Abnormal US 8/363(2.2%) patients, 1 or more tumor markers 9/363 (2.5%), chest radiograph 2/363 (0.55%), hemoccult test 16/363 (4.4%). CT was done in 46/363 (12.7%) patients.
- Occult lung, renal, colon and prostate cancers were diagnosed in 4/363 (1.1%) patients and 0/73 controls (p:ns)
- One study patient (0.27%) and 3 controls (4.1%) developed cancer over the follow-up ($p < 0.02$)
- No estrogen-dependent cancers
- Mean follow-up duration was 42.9±16.7 months in study patients and 50.6±18.1 in controls.

ANTI-TNFα AND CANCER CONCLUSIONS (1)

- Data from RCTs, Healthcare databases, National registries exclude a higher incidence of malignancies in p. receiving anti-TNFα compared to placebo and traditional DMARDs
- In RCTs 26.0% of malignancies occurred within 12 weeks from therapy starting indicating the need for a revision of the current cancer screening procedures

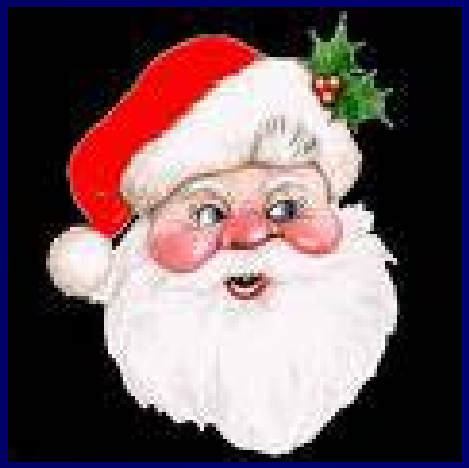
ANTI-TNFα AND CANCER CONCLUSIONS (2)

- Adopting more comprehensive screening procedures over a 5-year period we observed only 1 (0.27%) malignancy in 359 p. with a significant difference with respect to 3 (4.1%) cancers diagnosed in 73 controls
- Notably, these procedures allowed to detect occult cancer in 4 asymptomatic p. who would not have been excluded if screened only on the basis of "cancer or history of cancer"

GRAZIE PER L'ATTENZIONE

- Dott.ssa Laura Niccoli
- Dott.ssa Daniela Chindamo
- Dott. Emanuele Cassarà
- Dott.ssa Carlotta Nannini
- Dott. Michele Bertoni
- Dott. Giacomo Baccano

- Inf. Prof. Domenica Rochira
- Inf. Prof. Maddalena Fattibene
- Inf. Prof. Alessandra Bartolozzi
- Inf. Prof. Sabrina Guarducci
- Inf. Prof. Lorenza Marostica
- Inf. Prof. Donatella Cerofolini



NATALE 2008
AUGURI !!!