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**LAVORO ORIGINALE**

# MonitorNet: the Italian multi-centre observational study aimed at estimating the risk/benefit profile of biologic agents in real-world rheumatology practice

## *MonitorNet: studio italiano osservazionale multicentrico per la valutazione del profilo rischio-beneficio dei farmaci biologici nella pratica clinica reumatologica*

**P. Sfriso[1], F. Salaffi[2], C.M. Montecucco[3], S. Bombardieri[4], S. Todesco[5]**

*[1]Rheumatology Unit, University of Padova; [2]Department of Rheumatology, University of Ancona;*
*[3]President of the Italian Society of Rheumatology, Department of Rheumatology, University of Pavia;*
*[4]Past-President of the Italian Society of Rheumatology, Rheumatology Unit, University of Pisa;*
*[5]Principal Investigator research program AIFA FARM5KJ9P5, Rheumatology Unit, University of Padova, Italy*

**RIASSUNTO**

*MonitorNet è un database costituito dalla Società Italiana di Reumatologia (SIR) nel gennaio 2007 e finanziato dall'Agenzia Italiana del Farmaco (AIFA), con l'obiettivo del monitoraggio a lungo termine dei pazienti affetti da artrite reumatoide (AR), artrite psoriasica (AP) e spondilite anchilosante (SA) trattati con farmaci biologici. Tutte le Unità Operative Complesse di reumatologia italiane sono state invitate a partecipare ad uno studio epidemiologico, non-interventistico, osservazionale. Tale studio si svolge nell'ambito della pratica clinica quotidiana (real-world practice) dove i farmaci biologici sono prescritti sulla base delle raccomandazioni correnti. In questo articolo descriviamo il disegno e la metodologia dello studio e ne riportiamo i risultati preliminari. Al momento dell'analisi dei dati (Aprile 2009) il database comprendeva 3.510 pazienti: 2469 (70,3%) con AR, 675 (19,2%) con AP e 366 (10,4%) con SA. Il periodo cumulativo di follow-up era di 8.787 anni-paziente (AR: 8388, AP: 157, AS: 242). Sono stati riportati 1.538 eventi avversi in 938 (26,7%) pazienti. In 630 pazienti sono stati riportati episodi infettivi; in 142 reazioni avverse cutanee ed in 90 reazioni post-infusionali. Nel database sono state segnalate 30 neoplasie maligne. Un'analisi ad-interim dell'efficacia è stata condotta su 2.148 pazienti affetti da AR. In 731 pazienti (35,8%) è stata ottenuta la remissione secondo il criterio EULAR (DAS28<2,4). Utilizzando i parametri più restrittivi basati sugli indici CDAI e SDAI, la frequenza della remissione era più bassa (rispettivamente 17,9% e 14,7%). Il finanziamento di questo progetto ha fornito l'opportunità di organizzare una rete collaborativa nazionale di cliniche reumatologiche e di avviare un ampio studio osservazionale multicentrico.*

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## INTRODUCTION

Over the last decade, several new biologic agents have become available for the treatment of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and psoriasis (Ps). In contrast to conventional disease modifying anti-rheumatic drugs (DMARDs), these biological agents have rapid onset of action and pronounced disease reducing activity when administered as monotherapy or in combination with MTX. Pre-registration randomised clinical trials have compared biological agents against placebo over a limited time span (1-3). Wider use of biologics has resulted in reports of a wide range of adverse events (4), including evidence of reactivation of latent tuberculosis, increased incidence of other opportunistic infections and multiple sclerosis-like demyelinating disorders. With the introduction of these new therapeutic agents, it was apparent that

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*Indirizzo per la corrispondenza:*
Dott. Paolo Sfriso
Cattedra e UOC di Reumatologia
Università di Padova
Via Giustiniani 2 - 35128 Padova
E-mail: paolo.sfriso@unipd.it

longitudinal, long term, "real world" data would be of high value to the rheumatology community and the health authorities as well. Thus, by the time biologic agents were introduced in Italy, the Italian Health Authorities promoted a multicenter observational study (ANTARES) carried on by the Italian Society of Rheumatology (SIR) and the National Institute of Health (ISS) (5, 6). The main goals were to improve the knowledge of the population treated and to monitor drug effectiveness and safety in everyday practice.

The study started on June 2001 and data were collected until March 2004. At the beginning of the study only two biologic agents were approved for the treatment of patients with RA, e.g. etanercept and infliximab. Subsequently, anakinra and adalimumab received the approval of the Italian Health Authorities and TNF inhibitors' use expanded to other inflammatory disorders to include ankylosing spondylitis, psoriatic arthritis, and psoriasis as approved indications.

Given the particularity of biologics, which exert their action through a pharmacologically new selective mechanism, it has become increasingly clear that long-term surveillance systems continue to be needed to monitor effectiveness and their therapeutic window (7).

On this background, the Italian Medicines Agency (AIFA), approved and funded a study proposed by the Rheumatology Unit of the University of Padova along with SIR, ISS and GISED (Italian Group of Epidemiologic Studies in Dermatology) on the risk/benefit profile of biologic agents in real-world rheumatology and dermatology practice. The study, funded within the 2005 funding plan for independent research on drugs, is aimed at establishing a professional-based system to monitor effectiveness (i.e. efficacy, tolerability, safety, and patient compliance) of the biologic agents approved for the treatment of RA, PsA, AS and Ps. More specifically the objectives of the study are:

1) to evaluate the therapeutic attitude and identify the major factors that drive the choice of biologics;
2) to describe the long term outcome and safety profile of the different treatments;
3) to detect predictor factors of clinical response;
4) to identify patients at higher risk for adverse events and those for whom treatment is inadequate.

In the present report we describe the design, methodology, and present preliminary data of the rheumatological study.

## PATIENTS AND METHODS

### *The MonitorNet database*

MonitorNet is a database established by SIR in January 2007 and funded by AIFA for the active long-term follow-up of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis treated with biologic agents. All hospital Rheumatology Units in Italy were invited to participate in a non-interventional, observational, epidemiological study (post-marketing observational study) aimed at estimating the benefit/risk profile of the biologic agents.

Patients registered in MonitorNet are those with active rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis cared for by the participating centres who receive at least one dose of a prescribed biologic agents.

For each pathology, a concurrent control group of patients taking conventional therapies is enrolled. The study is conducted in a routine clinical setting (real-world practice) where biologics are prescribed on the basis of current recommendations. Exclusion criteria are limited to the contraindications stated in the Summary of Product Characteristics (SPC) of each drug.

### *Outcomes*

The primary outcomes for each study disease are: a) the proportion of responders to therapy; b) the number and frequency of adverse events. The secondary outcome is the retention in treatment. The maintenance on the originally administered therapy is evaluated as the number of days from therapy administration to the end of the study or the discontinuation of treatment (switch to another drug or study withdrawal).

### *Information retrieval*

All data are collected by each participating centre through a web-based data-base software. Information regarding patient demographics and characteristics, including co-morbidity and concomitant medication use, are recorded at baseline, defined as the time period just prior to initiation of treatment and during the follow-up.

Information on clinical and laboratory adverse events are recorded throughout the study at the scheduled time points for each disease, and whenever the patient report the occurrence of an adverse event. Complete disease and laboratory assessment are performed at baseline, at scheduled time points following study entry, and at exit from the study.

Assessment of the disease is performed using internationally established criteria:

a) Rheumatoid Arthritis: 1) the American College of Rheumatology (ACR) core set of outcome measures for rheumatoid arthritis; 2) the Disease Activity Score -DAS28; 3) SDAI and CDAI.
b) Ankylosing Spondylitis: 1) the Assessment in Ankylosing Spondylitis (ASAS) core set for daily practice; 2) the Bath Ankylosing Spondylitis Disease Activity Score -BASDAI; 3) the expert opinion.
c) Psoriatic Arthritis: 1) the ACR response criteria for evaluation of peripheral arthritis in PsA; 2) the Maastricht ankylosing spondilytis enthesis score-MASES; 3) the outcome variables outlined in the International ASAS consensus statement for the use of anti-TNF-alfa agents in AS.

***Time of evaluation and responder criteria***

Response to therapy is assessed at months 3, 6 and then every 6 months thereafter.

The following response criteria are used:

a) Rheumatoid Arthritis: DAS28 improvement, SDAI and CDAI;
b) ankylosing spondylitis: 50% relative or two-point absolute improvement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100-mm VAS) and expert opinion;
c) psoriatic arthritis with peripheral arthritis: 1) 20% reduction in the number of tender and swollen joints and 20% improvement of at least 3 of the remaining ACR20 criteria in patients with psoriatic polyarthritis (5 affected joints); 2) the response of patients with DMARD-resistant mono- or oligoarthritis at baseline is assessed on an individual basis; 3) expert opinion;
d) psoriatic arthritis characterized by enthesitis: 1) 20% reduction in the MASES in patients with 3 clinically inflamed entheses at baseline and 50% relative or two-point absolute improvement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100-mm VAS); 2) expert opinion;
e) psoriatic spondylitis: 1) 50% relative or two-point absolute improvement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100-mm VAS); 2) expert opinion.

***Planned statistical analysis***

Statistical analysis will be performed on 4,000 subjects after 30 months of total observational time. Analysis will be carried out for each different clinical condition (e.g. rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis). Descriptive statistics will include the number of observations, mean, standard deviation, minimum and maximum for continuous variables; count and percentages are provided in instances where the variables are categorical. Differences between categorical variables will be tested using Pearson's Chi2 test, and differences between continuous variables will tested using the one-way analysis of variance (ANOVA).

Multivariate regression models will be used. Evidence for effect modification will be investigated by first examining stratum specific OR or RR with homogeneity test results for the univariate analysis, and then by the inclusion of interaction terms within the multivariate regression model with Likelihood Ratio Tests of the null hypothesis of no interaction. To evaluate the goodness of fit for the logistic regression model will be used the Hosmer and Lemeshow's test. In addition to regression models the propensity score methodology will be used to deal with confounding caused by nonrandomized assignment of treatments in cohort studies.

***Safety***

Treatment emergent adverse events will be summarized using treatment counts and percentages by System Organ Class and WHO-ART category. The percentage of subjects experiencing an adverse drug reaction will also be provided for each treatment group and classified according to levels of severity and of causal relationship with the study drugs. A logistic regression model will be used to compare patients who experienced at least one ADR to those without ADRs. Crude incidence rates for ADR with 95% confidence intervals will be calculated from the total person-time exposure. The unadjusted rate ratios and ratios adjusted for selected risk factors plus confounding variables will be calculated and examined using both univariate methods and multivariate Poisson regression modelling.

***Effectiveness***

"Responders" to the therapy at different time points will be compared to "non-responders" using multivariate logistic regression models at a fixed time interval.

To identify subgroups of individuals sharing similar characteristics with differing probabilities of

outcome (responders/non responders) a regression tree approach will be also utilized.

***Retention in treatment***

Maintenance on the originally administered anti-TNF-alfa therapy will be evaluated as the number of days from therapy administration to the discontinuation of treatment. The probability of treatment maintenance will be estimated by Kaplan-Meier method. This will be performed for each biologic agent as well as for the total group. Drug survival between groups will be compared using the log rank test.

***Interim analysis***

Interim analysis is conducted every 6 months to assess trends in incidence of adverse events and to assess efficacy results.

***Ethical aspects***

The drugs involved are approved for the indications that are objects of the study and are available on the market. All the procedures used in this observational study are part of the usual care of the patients. Patient will be informed that his/her medical records will be anonymously utilised for this observational study and consent will be obtained.

## RESULTS

As of June 2009, a total of 3,627 patients from 31 centers had been registered in the MonitorNet database. Here we report an interim analysis of the first 3510 patients collected until April 2009.

At the time of the analysis, the database included 2469 (70.3%) patients with established RA, 675 (19.2%) with PsA and 366 (10.4%) with AS. The female:male ratio was 2.22 (2,420:1,090), mean age was 53.3±13.3 years (range 16-88). The cumulative follow up period was 8,787 patient-years (RA: 8,388, PsA: 157; AS: 242). Prior and actual DMARDs use is shown in Table I.

About 1,987 patients (56.6%) had at least one comorbidity; 587 patients (16.7%) had 2 comorbidity and 331 patients (9.4%) had 3 or more comorbidity.

Among 2464 patients who had taken only one biologic, 911 (37%) were treated with etanercept, 837 (34%) with adalimumab, 677 (27%) with infliximab, 14 (0.6%) with rituximab, 12 (0.5%) with anakinra and 6 (0.2%) with abatacept. Overall 680 patients switched to a second biologic and 214 patients used 3 or more biologic agents. There were 1,538 adverse events in 938 (26.7%) patients. These events were classified as mild in 30.9%, moderate in 49.7%, severe in 19.3% and life threatening in 0.1% of cases.

In Table II the classification of adverse events, according to the Rheumatology Common Toxicity Criteria v.2.0, is reported. There were infections in 630 patients, skin-related adverse events in 142 and post-infusion reactions in 90.

Urinary tract was the leading site of infection (173 patients) followed by the lower respiratory tract (152 patients). Six patients developed sepsis. The pathogens responsible for these infections were bacteria in 492 patients, viruses in 100, fungi in 37 and parasites in 1.

Among the microorganisms implicated in the infections mycobacterium tuberculosis was found in 9 patients, herpes zoster virus in 30 and herpes simplex virus in 18. A total of 30 malignancies were reported in the database, of which 19 were carcinoma, 7 were hematological neoplasia, 1 was Kaposi's sarcoma and 3 were melanoma (Table III).

**Table I -** Prior and actual DMARDs use in 3.510 patients.

| | *Prior* | | *Actual* | |
|---|---|---|---|---|
| *DMARD* | *N. of patients* | *%* | *N. of patients* | *%* |
| Methotrexate | 2033 | 57,9% | 2298 | 65,5% |
| Chloroquine/hydroxychloroquine | 797 | 22,7% | 167 | 4,8% |
| Leflunomide | 641 | 18,3% | 224 | 6,4% |
| Sulfasalazine | 725 | 20,7% | 85 | 2,4% |
| Cyclosporin | 525 | 15,0% | 39 | 1,1% |
| Gold salts | 265 | 7,5% | 2 | 0,1% |
| Azathioprine | 51 | 1,5% | 11 | 0,3% |
| Penicillamine | 20 | 0,6% | 0 | - |
| Colchicine | 7 | 0,2% | 2 | 0,1% |
| Cyclophosphamide | 6 | 0,2% | 0 | - |

**Table II -** Adverse events in 3.510 patients.

| | *Rheumatology Common Toxicity Criteria v.2.0* *Category* | *N. of events* |
|---|---|---|
| A | Allergic/immunologic | 105 |
| B | Cardiac | 65 |
| C | General | 204 |
| D | Dermatologic | 187 |
| E | Ear/nose/throat | 86 |
| F | Eye/ophthalmologic | 33 |
| G | Gastrointestinal | 186 |
| H | Musculoskeletal | 21 |
| I | Neuropsychiatric | 44 |
| J | Pulmonay | 206 |
| K | Haematology | 66 |
| L | Chemistry | 326 |
| M | Urinalysis | 9 |
| | Total | 1538 |

**Table III -** Malignancies in 3.510 patients.

| *Malignant neoplasm* | | *N.* | *%* |
|---|---|---|---|
| Carcinoma | | **19** | 0,541% |
| Not specified | 2 | | |
| Colon | 3 | | |
| Brest | 7 | | |
| Ovary | 1 | | |
| Lung | 2 | | |
| Kidney | 1 | | |
| Thyroid | 1 | | |
| Tonsil | 1 | | |
| Pancreas | 1 | | |
| Acute myeloid leukemia | | **1** | 0,028% |
| Lymphoma | | **6** | 0,171% |
| Large B-cell | 1 | | |
| Cutaneous | 1 | | |
| Non-Hodgkin's | 1 | | |
| Centrocytic non-Hodgkin's | 1 | | |
| Non-Hodgkin's B | 1 | | |
| Non-Hodgkin's CD20+ | 1 | | |
| Kaposi's sarcoma | | **1** | 0,028% |
| Melanoma | | **3** | 0,085% |
| Total | | **30** | 0,855% |

**Table IV -** disease activity assessment by composite indices in 2.148 RA patients treated with biologic agents after a mean follow-up of 23 months.

| | *DAS28* | *SDAI* | *CDAI* |
|---|---|---|---|
| Still active | 61,7% | 59,1% | 55,7% |
| Minimal disease activity | 2,5% | 26,2% | 26,4% |
| Remission | 35,8% | 14,7% | 17,9% |

DAS28: minimal disease activity <2.85; remission <2.4. SDAI: minimal disease activity <11; remission <3.3. CDAI: minimal disease activity <10; remission <2.8.

An interim analysis of efficacy was conducted on 2,148 RA patients based on data available as of April 6 2009. Seven hundred and thirty-one patients (35.8%) achieved EULAR remission (defined as DAS28<2.4). When assessed with the more restrictive CDAI and SDAI criteria, the frequency of remission was lower (17.9% and 14.7% respectively) (Table IV).

## DISCUSSION

While biological agents targeting TNF-alfa, IL-1 and T-cells have proved to be effective in the treatment of RA, PsA, AS, and psoriasis, however, rare-to-uncommon and unexpected toxicities have been found and other may yet be found during their use. True population-based cohort studies in selected areas of efficacy, toxicity and general use of these biologics are needed to help further define the most appropriate use of these agents.

AIFA is a governmental institution operating within the Italian Ministry of Health in collaboration with Regional Health Authorities. AIFA activities include, among the others, marketing authorisation of medicinal products, pharmacovigilance, monitoring of clinical trials, drug expenditure governance. The promotion of independent research on drugs represents one of the strategic tasks assigned to AIFA by legislation. Within the funding plan for independent research on drugs, AIFA funded the present study aimed at monitoring the effectiveness of the biologic agents approved for the treatment of RA, PsA, AS and Ps.

In this report we describe the design and methodology, and present preliminary data of MonitorNet, a multi-centre observational study on the risk/benefit profile of biologic agents in real-world rheumatology practice.

Randomized controlled trials represent an efficient design to assess drug efficacy and to detect common, immediate side-effects in pre-selected patient populations. However, typical trial procedures assure internal validity of results but often limit their generalizability. In fact, patients are usually enrolled through restrictive eligibility criteria (e.g. lack of serious concomitant illnesses) and receive better care, even in the placebo arm, than any patient in the real world. Moreover, not frequent or long term adverse drug reactions can hardly be observed. There is not only a concern for patient populations normally excluded by clinical studies on efficacy and safety, such as pregnant women and

the elderly. There is also a need to obtain more information on research issues less explored in commercial research, such as clinically relevant end points, comparative studies and long term follow up on efficacy and safety of therapies.
During a cumulative follow up period of 8,787 patient-years no new safety concerns were identified in our cohort. In particular, as regard opportunistic pathogens, the crude incidence rates of mycobacterium tuberculosis and herpes zoster virus infection were 1.02 and 3.41 cases per 1,000 patient-years respectively. To date, 6 lymphoma and 24 other malignancies were reported in the database. The respective crude incidence rates were 0.68 and 2.73/1,000 patient-years.
Since biologic response modifiers have been proved to markedly reduce signs and symptoms of the disease, better outcomes are expected, and remission has become the goal of RA therapy (8). However there are only few reports of efficacy of biological drugs outside clinical trials. The percentage of patients who achieved an EULAR remission in our cohort (35.8%) is similar to that recently reported in the nationwide Danish DANBIO Registry from the year 2004 to the year 2005 cohort (37% and 38% respectively) (9).
In the large prospective observational LORHEN registry (10) 29.9% of RA patients was classified as being in EULAR remission after 14.5 months of anti-TNF therapy. These results are similar to those found in randomized clinical trials (11-18) as well as in the British registry (19), but contrast to the GISEA retrospective cohort study on longstanding RA starting anti-TNF therapy that shows lower DAS28 remission rate (20). In the latter study, however, only 54.25% of the 1,257 enrolled patients continued their therapy up to the sixth month. As a consequence, considering all the enrolled patients, DAS28 remission was reached in about 12% RA patients.
The impressive achievement*s* in controlling RA have needed parallel development of the methods suitable to assess the results of the new medications. Adequate instruments to define remission in RA have been proposed on the basis of patients' follow-up both in trials and in clinical practice (21, 22). DAS28 seems to be well suited for use in clinical practice. On the other hand simplified joint count could lead to underestimate the disease as it is not considering ankles and joints of feet. Evidence has been found that the remission achievement rate depends on score employed in clinical trials. DAS28 criteria have proved to have significantly higher response rates, when compared to other criteria (23-25). The CDAI and SDAI criteria for remission appear to be more stringent with lower rate of patients meeting the remission definition and being therefore more specific and less prone to false positives qualifications than other scores (26).
Residual joint count in patients in SDAI/CDAI remission revealed that these indices allow only a minimal number of swollen and tender joints (27). Indeed, successful long term use of TNF inhibitors and other biologic agents require ongoing monitoring to confirm efficacy (and continued need) and avoid drug toxicity.
Availability of funding for this study provides, for the first time in our Country, an opportunity to organize a collaborative national network of rheumatology, and dermatology clinics to develop a large multicentre observational study. The results of this study will contribute to establish the long term outcome and safety profile of the different biologic agents in the real-world rheumatology and dermatology practice.

### *Appendix A: Contributors to the MonitorNet Database*

In addition to the authors, the following investigators (and their centers) are contributors to the MonitorNet database in decreasing order of the number of patients enrolled: Prof. Mauro Galeazzi, (Siena); Dott. Piercarlo Sarzi-Puttini, (Milano); Prof. Flavio Fantini, (Milano); Prof. Carlomaurizio Montecucco, (Pavia); Prof. Roberto Cattaneo, (Brescia); Prof. Leonardo Punzi, (Padova); Prof. Stefano Bombardieri, (Pisa); Dott. Flavio Mozzani, (Parma); Prof. Alessandro Mathieu, (Cagliari); Prof. Guido Valesini, (Roma); Prof. Valentini Gabriele, (Napoli); Prof. Clodoveo Ferri, (Modena); Prof. Lisa Maria Bambara, (Verona); Prof. Walter Grassi, (Ancona); Prof. Francesco Trotta, (Ferrara); Prof. Roberto Gerli, (Perugia); Prof. Silvano Adami, (Valeggio-VR); Prof. Giovanni Lapadula, (Bari); Prof. Raffaele Pellerito, (Torino); Prof. Salvatore De Vita, (Udine); Prof. Giovanni Minisola, (Roma); Dott. Rosario Foti, (Catania); Dr. Giuseppe Paolazzi, (Trento); Prof. GianFilippo Bagnato, (Messina); Prof. Maurizio Cutolo, (Genova); Dott. Pier Andrea Rocchetta, (Alessandria); Prof. GianFranco Ferraccioli, (Roma); Dott.ssa Bianca Anna Canesi, (Milano); Prof. Marco Matucci-Cerinic, (Firenze); Dott. Modena Vittorio, (Torino); Dott. Marco Canzoni, (Roma).

**SUMMARY**

MonitorNet is a database established by the Italian Society of Rheumatology (SIR) in January 2007 and funded by the Italian Medicines Agency (AIFA), for the active long-term follow-up of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis treated with biologic agents. All hospital Rheumatology Units in Italy were invited to participate in a non-interventional, observational, epidemiological study. The study is conducted in a routine clinical setting (real-world practice) where biologics are prescribed on the basis of current recommendations. In this report we describe the design, methodology, and present preliminary data of the study. At the time of the analysis (April 2009) the database included 3510 patients: 2469 (70.3%) with established RA, 675 (19.2%) with PsA and 366 (10.4%) with AS. The cumulative follow up period was 8,787 patient-years (RA: 8,388, PsA: 157; AS: 242). There were 1,538 adverse events in 938 (26.7%) patients. Infections were recorded in 630 patients, skin-related adverse events in 142 and post-infusion reactions in 90. A total of 30 malignancies were reported. An interim analysis of efficacy was conducted on 2,148 RA patients. Seven hundred and thirty-one patients (35.8%) achieved EULAR remission (defined as DAS28<2.4). When assessed with the more restrictive CDAI and SDAI criteria, the frequency of remission was lower (17.9% and 14.7% respectively). Availability of funding for this study provided an opportunity to organize a collaborative national network of rheumatology clinics to develop a large multicentre observational study.

**Parole chiave** - Farmaci biologici, anti-TNF, studio osservazionale, efficacia, sicurezza, pratica clinica.
***Key words*** *- Biological agents, anti-TNF, observational study, efficacy, safety, real-world practice.*

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