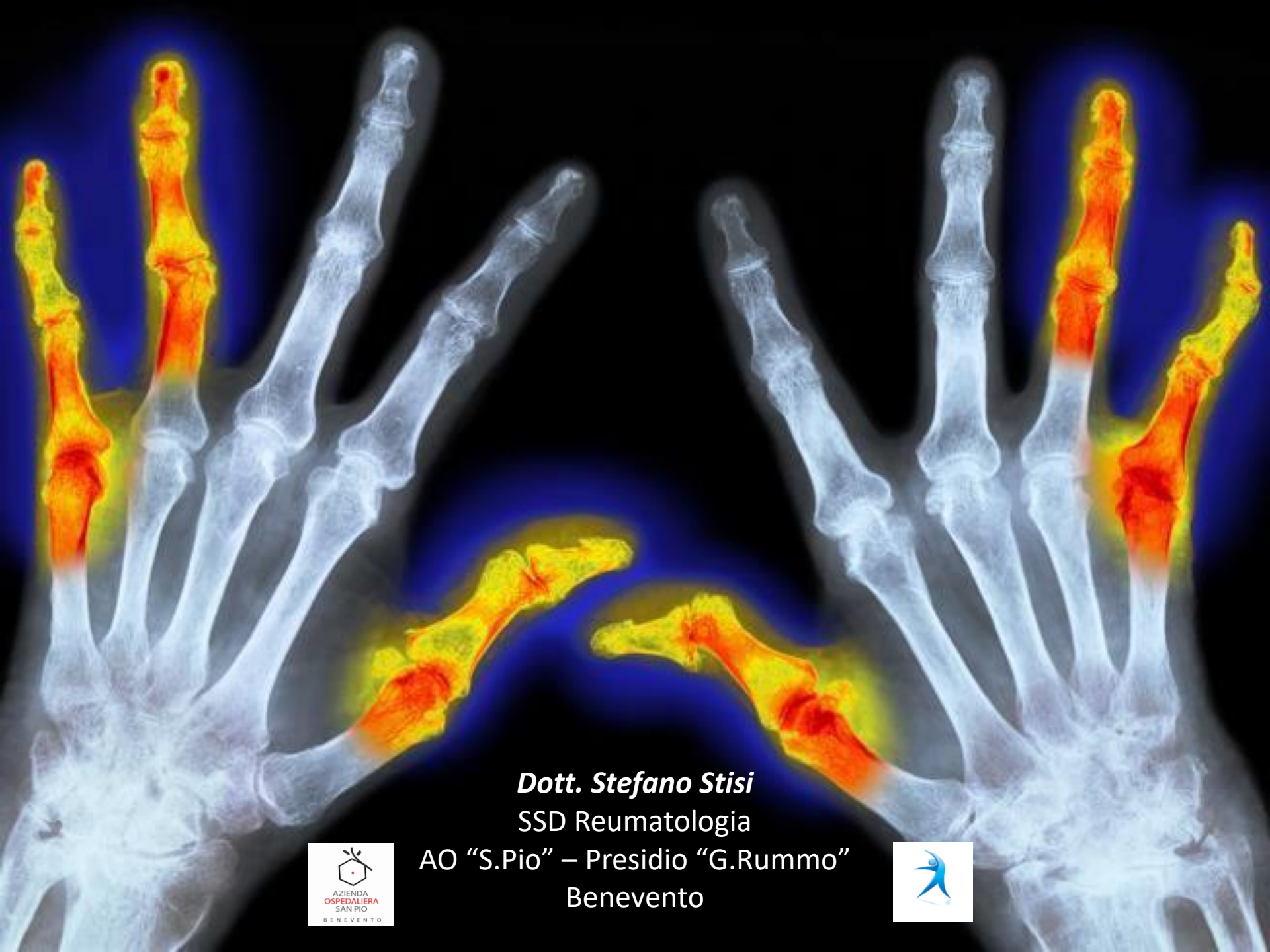
L'ALLEANZA CLINICO-FARMACISTA NELLA GESTIONE DELLA CRONICITÀ: IL CASE STUDY ARTRITE REUMATOIDE

NAPOLI, 15 novembre 2018

Il fenomeno della sottodiagnosi e del sottotrattamento



Dott. Stefano Stisi
SSD Reumatologia
AO “S.Pio” – Presidio “G.Rummo”
Benevento

Il fenomeno della sottodiagnosi in AR

Sottodiagnosi

DIAGNOSI corretta

Sovradiagnosi

ARTHRITIS & RHEUMATISM
Vol. 62, No. 9, September 2010, pp 2569–2581
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Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

Daniel Aletaha,[1] Tuhina Neogi,[2] Alan J. Silman,[3] Julia Funovits,[1] David T. Felson,[2] Clifton O. Bingham, III,[4] Neal S. Birnbaum,[5] Gerd R. Burmester,[6] Vivian P. Bykerk,[7] Marc D. Cohen,[8] Bernard Combe,[9] Karen H. Costenbader,[10] Maxime Dougados,[11] Paul Emery,[12] Gianfranco Ferraccioli,[13] Johanna M. W. Hazes,[14] Kathryn Hobbs,[15] Tom W. J. Huizinga,[16] Arthur Kavanaugh,[17] Jonathan Kay,[18] Tore K. Kvien,[19] Timothy Laing,[20] Philip Mease,[21] Henri A. Ménard,[22] Larry W. Moreland,[23] Raymond L. Naden,[24] Theodore Pincus,[25] Josef S. Smolen,[1] Ewa Stanislawska-Biernat,[26] Deborah Symmons,[27] Paul P. Tak,[28] Katherine S. Upchurch,[18] Jiří Vencovský,[29] Frederick Wolfe,[30] and Gillian Hawker[31]

This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

The American College of Rheumatology is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.

Perché da evitare la sottodiagnosi?

- Over the last decade, the optimal use of disease modifying antirheumatic drugs have dramatically enhanced the success of RA management.
- Undoubtedly, treating patients at a stage at which evolution of joint destruction can still be prevented would be ideal.
- However, at present, clinical trials of RA treatments are hampered by lack of criteria allowing for study enrollment of patients at **early stages** of disease. Thus, to date it has not been possible to effectively investigate the efficacy of early interventions in terms of their ability to prevent later-stage RA, since there are no validated or accepted uniform criteria to classify such individuals with early disease.

Aletaha et al, 2010 Rheumatoid Arthritis Classification Criteria. ARTHRITIS & RHEUMATISM Vol. 62, No. 9, September 2010, pp 2569–2581

Criteri classificativi ACR-EULAR 2010

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

Diagnose early and very early rheumatoid arthritis

- Early rheumatoid arthritis (RA) and very early RA are major targets of research and clinical practice. Remission has become a realistic goal in the management of RA, particularly in early disease.
  - The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) **RA classification criteria**,
  - the **EULAR treatment recommendations for RA**, and
  - the **EULAR recommendations for the management of early arthritis** focus on early disease and translate the knowledge related to early RA into classification and management.

Zeidler H. The need to better classify and diagnose early and very early rheumatoid arthritis. J Rheumatol. 2012 Feb;39(2):212-7

Diagnose early and very early rheumatoid arthritis

- Nevertheless, there is a need for further improvement and progress. Results from 6 recent studies are summarized, evaluating the performance of the 2010 ACR/EULAR RA classification criteria.
- The data show a significant risk of misclassification, and highlight that **overdiagnosis and underdiagnosis** may become important issues if the criteria recommend synthetic and biological disease-modifying antirheumatic drugs. The possible effect of misclassification on spontaneous and drug-induced remission of early and very early RA awaits further elucidation. Such research will eventually lead to more reliable diagnostic and classification criteria for new-onset RA.

Zeidler H. The need to better classify and diagnose early and very early rheumatoid arthritis. J Rheumatol. 2012 Feb;39(2):212-7

How are the new criteria performing in the clinic?

- The objective of the 2010 ACR/European League Against Rheumatism classification criteria for RA was to distinguish patients at high risk for developing persistent erosive and/or inflammatory disease from those with undifferentiated inflammatory arthritis.
- These criteria were developed for use in clinical trials; in order to implement these criteria most effectively, they need to be validated in real-world settings.
- The 1987 criteria may have led to underdiagnosis in the case of patients with positive anti-citrullinated peptide antibody values but no evidence of radiographic progression of joint erosion, or overdiagnosis in the case of some patients with FM; similarly, the possibility that the 2010 criteria may result in **overdiagnosis** cannot be excluded.

Bykerk VP, Massarotti EM. The new ACR/EULAR classification criteria for RA: how are the new criteria performing in the clinic? Rheumatology (Oxford) 2012 Dec;51 Suppl 6

How are the new criteria performing in the clinic?

- Prospective validation of the 2010 criteria has been carried out in several cohorts, with reported sensitivities ranging from 0.50 to 0.60 and specificities from 0.88 to 0.97. The sensitivity and specificity of the 2010 criteria were 0.74 and 0.66 when compared against the gold standard of needing MTX therapy in the opinion of experienced clinicians, and 0.69 and 0.72 against the standard of having persistent synovitis despite DMARDs after 1 year.
- Other comparisons have yielded similar sensitivities and specificities, ranging up to 0.85 for the gold standard of needing MTX therapy. Questions remain concerning the utility of the 2010 criteria for non-arthritis **health care practitioners, who may be less than expert in identifying swollen joints and may underestimate the number of joints affected by synovitis**.

Bykerk VP, Massarotti EM. The new ACR/EULAR classification criteria for RA: how are the new criteria performing in the clinic? Rheumatology (Oxford) 2012 Dec;51 Suppl 6

Reduce CV risk in patients with RA

Cardiovascular Risk in Rheumatic Patients: The Link between Inflammation and Atherothrombosis

Matteo Nicola Dario Di Minno, M.D.[1] Salvatore Iervolino, M.D.[2] Roberta Lupoli, M.D.[1] Anna Russolillo, M.D.[1] Antonio Coppola, M.D.[1] Rosario Peluso, M.D.[2] Raffaele Scarpa, M.D.[2] Giovanni Di Minno, M.D.[1]

[1] Department of Clinical and Experimental Medicine, Regional Reference Center for Coagulation Disorders, Federico II University, Naples, Italy
[2] Department of Clinical and Experimental Medicine, Rheumatology Research Unit, Psoriatic Arthritis Clinic, Federico II University, Naples, Italy

Address for correspondence and reprint requests Matteo Nicola Dario Di Minno, M.D., Department of Clinical and Experimental Medicine, Regional Reference Center for Coagulation Disorders, "Federico II" University, Via S. Pansini 5, 80131 Naples, Italy (e-mail: dario.diminno@hotmail.it).

Semin Thromb Hemost 2012;38:497–505.

Abstract

In addition to a high prevalence of the metabolic syndrome and a significant underdiagnosis of vascular risk factors (VRFs), the effect of chronic inflammation also represents the cornerstone of the raised cardiovascular (CV) risk in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Moreover, the finding that among current anti-inflammatory treatments, the use of tumor necrosis factor (TNF)-α blockers is associated with optimal rheumatologic and CV outcomes further supports the impact of inflammation on the CV risk. However, up-to-date treatment guidelines suggest that TNF-α blockers should be used only after the failure of traditional disease-modifying antirheumatic drugs (DMARDs). Early predictors of the therapeutic efficacy of traditional DMARDs are needed to identify candidates for TNF-α blocker treatment. Furthermore, whether the CV risk should be taken into account while choosing antirheumatic treatments is an emerging issue to be addressed. Common educational programs for specialists and general practitioners and appropriate CV prevention programs, taking into consideration traditional VRFs as well as the inflammatory status, should be planned to prevent ischemic events and to achieve optimal inflammation control in rheumatic patients.

Keywords
- cardiovascular risk
- rheumatoid arthritis
- psoriatic arthritis
- ankylosing spondylitis

Together with the progressive disability secondary to the joint impairment, cardiovascular (CV) risk is a major issue in patients with rheumatic diseases.[1] In this clinical setting, a high prevalence of the metabolic syndrome (MetS) and of its major features (obesity, hypertension, impaired fasting glucose, hypercholesterolemia, hypertriglyceridemia) have been described.[2] However, such an association does not entirely explain the extent of premature atherosclerosis in rheumatic subjects and inflammation appears to act synergistically with traditional vascular risk factors (VRFs), thus contributing to the atherosclerotic process and to the increased CV risk.[3,4] Monocytes, CD4+ T-lymphocytes and most proinflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, and IL-18) play a central role in the pathophysiology of major arthritides,[5] and are involved in the induction and in the maintenance of the atherosclerotic process

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Issue Theme Thrombotic and Hemorrhagic Syndromes Associated with Autoimmunity and Infection; Guest Editors, Massimo Franchini, M.D., Antonio Coppola, M.D., Marcel Levi, M.D., Ph.D., and Emmanuel J. Favaloro, Ph.D., M.A.I.M.S., F.F.Sc. (RCPA).

DOI http://dx.doi.org/10.1055/s-0032-1306433.
ISSN 0094-6176.

- Furthermore, whether the CV risk should be taken into account while choosing antirheumatic treatments is an emerging issue to be addressed.

Sottodiagnosi e sottotrattamento

Aggressive rheumatoid arthritis registry in Italy. Characteristics of the early rheumatoid arthritis subtype among patients classified according to the ACR criteria

Gruppo Italiano Artrite Reumatoide Aggressiva (GIARA)
Clin Exp Rheumatol. 2003 Sep-Oct;21(5 Suppl 31):S129-32

- The major conclusion of this preliminary analysis is that an overall tendency to undertreatment is discernable.

The Italian registry of aggressive rheumatoid arthritis - the GIARA project

- In 1999, the Italian Society of Rheumatology started a project to determine the prevalence and clinical characteristics of aggressive rheumatoid arthritis (ARA).
- For 1 year, all patients with RA for > 5 years and referred to participating centers were entered in a registry and classified as having ARA if they fulfilled the following criteria:
  - 10 swollen joints for at least 6 weeks, positive rheumatoid factor (RF), and at least one bone erosion (if disease duration of 2 years); (a) RF-positive and having 10 swollen joints or at least one newly eroded joint, or (b) if RF-negative, having 10 swollen joints and at least one newly eroded joint (if disease duration > 2 to < 5 years).

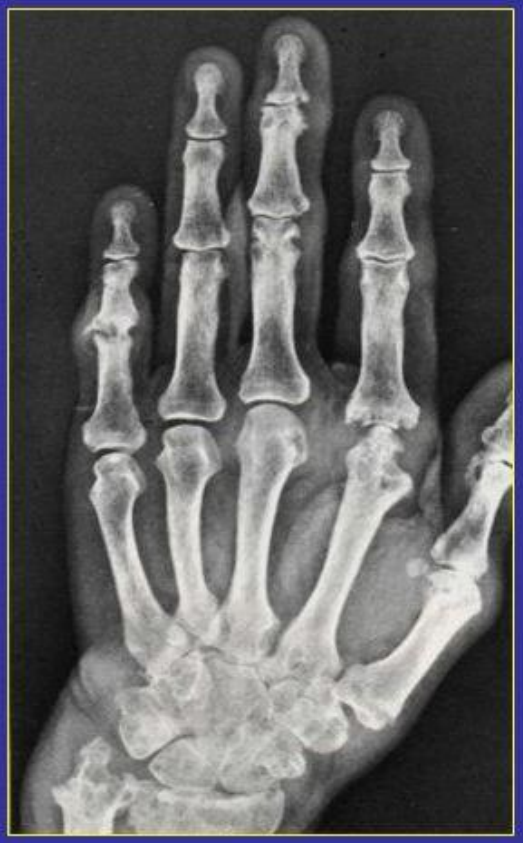
Marchersoni A et al. The Italian registry of aggressive rheumatoid arthritis - the GIARA project. J Rheumatology 2007 Dec;34(12):2374-81

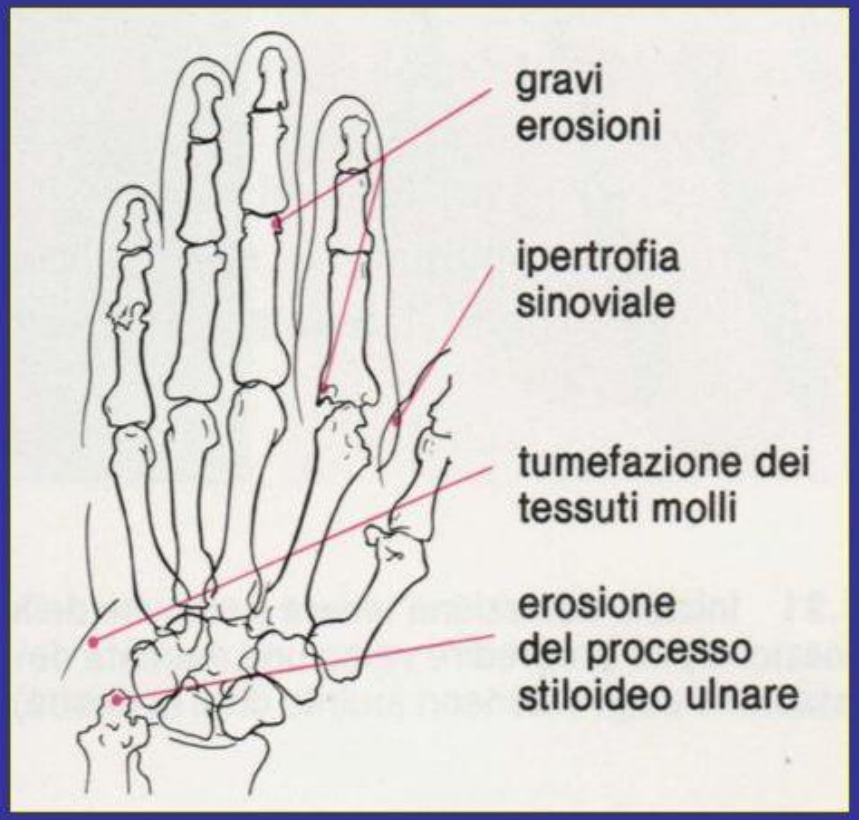
The Italian registry of aggressive rheumatoid arthritis - the GIARA project

- The frequency of ARA was 15% in the 2-year group and 63% in the > 2 to < 5-year group, but 35% of the patients in the 2-year group had erosions. Bone erosions were associated with disease duration, a Health Assessment Questionnaire value > 1.5, female sex, and RF positivity.
- In an Italian RA population, the GIARA (Gruppo Italiano Artrite Reumatoide Aggressiva) **criteria for ARA were met by 15% of the patients with disease duration of 2 years, but erosions were seen in 35%.** Upon referral, **most of the RA patients were inadequately treated** and had other conditions.

Marchersoni A et al. The Italian registry of aggressive rheumatoid arthritis - the GIARA project. J Rheumatology 2007 Dec;34(12):2374-81

Erosioni articolari





ACCESSO ALLE TERAPIE CON FARMACI BIOLOGICI:

i fenomeni di sottotrattamento e le opportunità offerte dai biosimilari

27 marzo, ore10
Roma Eventi Trevi
Piazza della Pilotta, 4
00187 Roma

Tavolo 2 – Area clinica della Reumatologia

Facilitatore

Guido Valesini

(Società Italiana Reumatologia – SIR)

Partecipanti

Antonella Celano *(Presidente Associazione nazionale persone con Malattie Reumatologiche e Rare - APMAR)*

Roberto Gorla *(AO Spedali Civili di Brescia)*

Carlo Maurizio Montecucco *(Collegio dei Presidenti Emeriti Società Italiana Reumatologia – SIR)*

Giuseppe Nocita *(SUMAI)*

Stefano Stisi *(Presidente Collegio Reumatologi Italiani - CREI)*

Silvia Tonolo *(Presidente Associazione nazionale Malati Reumatici ONLUS - ANMAR)*

Francesca Tosolini *(Regione Friuli Venezia Giulia)*

Francesco Deligios (*Ernst & Young)*

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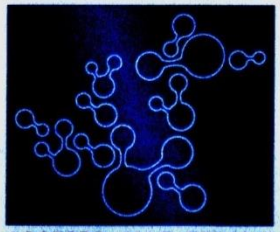
TUTELA RICERCA E SVILUPPO PER LA SALUTE



ACCESSO ALLE TERAPIE CON FARMACI BIOLOGICI:
i fenomeni di sottotrattamento e le opportunità offerte dai biosimilari

Tavolo 2- Area Clinica della Reumatologia

AR sottotrattamento

Artrite Reumatoide - Background

Definizione

L'**artrite reumatoide** è una malattia infiammatoria cronica, sistemica ed invalidante che colpisce la **membrana sinoviale** delle ***articolazioni***, che aumenta di volume e invade la ***cartilagine***, provocandone l'**erosione** e la **graduale distruzione**. Questo processo proliferativo si estende all'osso e alle articolazioni fino a colpire l'**intero organismo**, in particolare occhi, polmoni, cuore e reni[1].

Prevalenza

In Italia ci sono circa ***200.000 pazienti*** prevalenti con artrite reumatoide (circa lo **0,33% della popolazione**)[2].

Trattamento con biologici

Nell'**artrite reumatoide** i farmaci biologici sono utilizzati[3] al verificarsi congiunto delle seguenti condizioni: in ***seconda linea*** dopo il **fallimento dei o intolleranza ai cDMARD e tsDMARD**[1] e con ***malattia in fase attiva*** o con ***danno strutturale progressivo***.

1) Associazione Italiana Reum Amici (A.I.R.A.), «Cosa è l'artrite reumatoide»
2) Lucioni et al., 2015
3) Linee guida EULAR, 2016

EY

AR sottotrattamento

Artrite Reumatoide - Trattamento

200.000 prevalenti

Pazienti eleggibili a biologico	Pazienti trattati con biologico	Pazienti in sottotrattamento con biologico
58.000 MAX 43.000 MIN	38.000	MAX 20.000 MIN 5.000
In Italia circa **58.000 pazienti**[4] con **artrite reumatoide** sono eleggibili al trattamento con biologico. Secondo un confronto con **KOL** tale dato si abbasserebbe a circa **43.000** pazienti	Tuttavia si stima che solo **38.000** pazienti siano **effettivamente trattati**[5]	Come conseguenza, in Italia si stimano circa **20.000 pazienti** affetti da **artrite reumatoide** in **sottotrattamento. Considerando l'esperienza del KOL**, tale dato si **potrebbe abbassare a 5.000** pazienti

Costo dei biologici?

Ritardo di ingresso al percorso di cura presso il reumatologo?

Accentramento dei centri specialistici?

Impossibilità di prescrizione per le farmacie territoriali?

4) Censis-ANMAR-SIR (2008). «Primo rapporto sociale sull'artrite reumatoide»
5) AIB split (dati IQVIA)

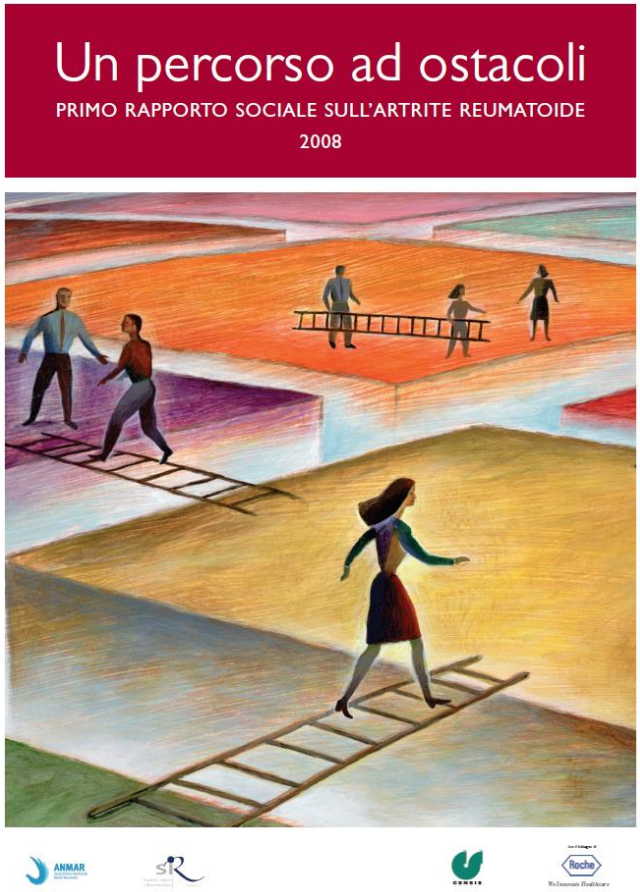
EY

OUTPUT 1 - Percezione del fenomeno del sottotrattamento

Qual è la percezione del Tavolo circa il fenomeno del sottotrattamento dei farmaci biologici, da ben distinguere rispetto ai fenomeni di sottodiagnosi e ritardo di primo accesso alla cura, rispetto alle stime fornite nello studio E&Y?

Percezione di sottostima
Dati non precisi

Fonti discutibili



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ORIGINAL ARTICLE
Open Access

Analisi di budget impact del biosimilare di infliximab: lo scenario italiano

Carlo Lucioni[1], Silvio Mazzi[1], Roberto Caporali[2]

[1] Health Publishing & Services, Milano - Italy
[2] Università di Pavia e Fondazione IRCCS Policlinico San Matteo, Pavia - Italy

Budget impact analysis of infliximab biosimilar: the Italian scenery
Chronic inflammatory diseases, while seriously impairing patients' quality of life, are a heavy financial cost to the National Health Service (NHS) and to society. The availability of biological drugs – among which infliximab (Remicade®) – greatly improved treatment efficacy. On the other hand, these drugs are an expensive resource. Infliximab patent protection is going to expire, and a biosimilar has been recently approved.
A budget impact (BI) analysis was conducted to evaluate the favourable consequences – for the Italian NHS – of the biosimilar availability in terms of cost containment (savings), thanks to its lower price compared to the originator's. The analysis model expects that some patients in treatment with the originator will switch (according to a prudent assumption of the market uptake rate) to the biosimilar and that many naïve patients will directly start treatment with the biosimilar (according to a bolder uptake rate assumed). Separately considering all the different diseases for which infliximab is indicated, the number of patients who might potentially use the biosimilar is estimated – based on disease prevalence and incidence rates, the overall proportion of treated patients and the infliximab market share. The time horizon extends to five years (starting from 2015). The biosimilar price discount is 25%.
The results from the analysis show (in the base case) that the availability of the biosimilar would provide overall annual savings over €16 million to the NHS in 2019, while the cumulated savings in the five years period would be no less than €47 million. The sensitivity analysis highlights that such favourable results would be even more substantial, to the extent that switching from originator to biosimilar could be safely recommended.
Keywords: Budget Impact, Infliximab, Biosimilar

Introduzione e obiettivi

Le malattie infiammatorie croniche, a eziopatogenesi autoimmune, si caratterizzano per l'importante disabilità che arrecano ai pazienti, determinando gravi conseguenze sulla qualità di vita degli stessi. Va inoltre considerato che, essendo per definizione patologie croniche, rappresentano un considerevole onere per i Servizi Sanitari Nazionali (SSN) a causa degli elevati costi di trattamento, che assorbono una parte importante delle risorse disponibili per la tutela della salute di un Paese (1).

Rientrano in questo gruppo di malattie l'artrite reumatoide (AR), la spondilite anchilosante (SA), la malattia di Crohn (MC), la colite ulcerosa (CU), l'artropatia psoriasica (AP) e la psoriasi (Ps). Il grado di disabilità di tali patologie, elevato sin dalle fasi iniziali, incide pesantemente sulla qualità della vita non solo del paziente, ma anche dei suoi familiari e più in generale delle persone che se ne occupano (2). Si tratta pertanto di malattie a forte impatto sociale; la parte prevalente dei costi di queste malattie è costituita dalle assenze dal posto di lavoro (molti pazienti abbandonano precocemente l'attività lavorativa) e dalle cure informali fornite su base volontaria dai caregiver, cioè l'assistenza fornita al paziente non contemplata dal SSN o da operatori privati (3). Si stima che i costi diretti sanitari rappresentino meno della metà del totale, come per la quasi totalità delle malattie cronico-degenerative (4-6).

L'incidenza e la prevalenza di queste malattie non sono particolarmente elevate, con l'eccezione della Ps, ma nel loro insieme rappresentano nel panorama italiano una frazione non secondaria della popolazione. Prevalenze più elevate si riscontrano, per alcune di esse, nei Paesi del Nord Europa (7). Applicando dati di prevalenza alle popolazioni di Regno Unito, Germania, Italia, Paesi Bassi e Belgio, si può stimare che quasi sette milioni di pazienti siano affetti da tali patologie.

I trattamenti farmacologici a oggi non determinano la guarigione, ma possono permettere lo stato di remissione o una bassa attività di malattia. L'avvento dei farmaci biologici sul finire degli anni novanta, e in particolare di infliximab (1999), il primo anticorpo monoclonale, inibitore del *tumor necrosis factor*-α (anti TNF), ha cambiato la storia del trattamento di

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Indirizzo per la corrispondenza:
Carlo Lucioni
Health Publishing & Services Srl
Piazza Duca d'Aosta 12
20124 Milano, Italy
clucioni@aboutpharma.com

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*de Waure C, Sferrazza A, Gualano MR, et al. Epidemiologia e burden of disease dell'artrite reumatoide. Ital J Public Health. 2010;7(Suppl 2):S3-13.

OUTPUT 3 - Gap informativo

Quali dati o strumenti sarebbero necessari allo scopo di meglio definire il fenomeno del sottotrattamento;

Indagini epidemiologiche

OUTPUT 4 - Cause alla base dei fenomeni di sottotrattamento

Lo studio E&Y ha ipotizzato alcune cause alla base dei fenomeni di sottotrattamento. Quali possibili ulteriori cause possono essere individuate per descrivere il fenomeno del sottotrattamento?

Carenza di centri e specialisti territoriali di Reumatologia

Percorsi

OUTPUT 5 - Possibili soluzioni al sottotrattamento

Quali strumenti, strategie ed approcci possono essere individuati al fine di ridurre il fenomeno di sottotrattamento e o mancato/ritardato accesso alle terapie con biologici.

Creazioni di rete

Conclusioni a chiusura del tavolo AIFA

1. C’è necessità, prima di parlare di sottotrattamento dell’artrite reumatoide, di studi epidemiologici diretti ed aggiornati.
2. AIFA si impegna a proporre al Ministero di attivare appositi studi - attraverso le Società Scientifiche dei reumatologi italiani (SIR e CReI) - per verificare l’ipotesi di sottotrattamento.