Approcci interdisciplinari in reumatologia 4a edizione *Infettivologia e malattie reumatiche*

Profilassi: come e quando: P. Jirovecii e altri miceti in reumatologia

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Lezione dall'HIV

Storia naturale dell'infezione da HIV

Patogenesi HIV

HAART

Highly active antiretroviral therapy

- HAART: ricostituzione immunitaria (incremento linfociti CD4+), abbattimento VL (dove possibile…), riduzione rischio malattie opportunistiche

Qual'é il reale rischio di manifestazione di infezione fungina?

	Scala del pericolo	Stabilità del manto nevoso	Probabilità di distacco di valanghe
1	DEBOLE	Il manto nevoso è in generale ben consolidato oppure a debole coesione e senza tensioni.	Il distacco è generalmente possibile solo con forte sovraccarico su pochissimi punti sul terreno ripido estremo. Sono possibili scaricamenti e piccole valanghe spontanee.
2	MODERATO	Il manto nevoso è moderatamente consolidato su alcuni pendii ripidi, per il resto è ben consolidato.	Il distacco è possibile soprattutto con un forte sovraccarico soprattutto sui pendii ripidi indicati. Non sono da aspettarsi grandi valanghe spontanee.
3	MARCATO	Il manto nevoso presenta un consolidamento da moderato a debole su molti pendii ripidi.	Il distacco è possibile con debole sovraccarico soprattutto sui pendii ripidi indicati. In alcune situazioni sono possibili valanghe spontanee di media grandezza e, in singoli casi, anche grandi valanghe.
4	FORTE	Il manto nevoso è debolmente consolidato sulla maggior parte dei pendii ripidi.	Il distacco è probabile già con un debole sovraccarico su molti pendii ripidi. In alcune situazioni sono da aspettarsi molte valanghe spontanee di media grandezza e, talvolta, anche grandi valanghe.
5	MOLTO FORTE	Il manto nevoso è in generale debolmente consolidato e per lo più instabile.	Sono da aspettarsi molte grandi valanghe spontanee, anche su terreno moderatamente ripido.

Variabilità di sindromi

Eziopatogenesi differenti (non sempre nota)

DMARD (disease-modifying anti-rheumatic drug) therapy

- MTX
- Idrossiclorochina
- Sulfasalazina
- Azatioprina
- Leflunamide

Anticorpi monoclonali

Table 1. Description of the monoclonal antibodies, their indications, mechanism of action, dosing, and corresponding pivotal trials

DRUG (year approved by US FDA)	FDA-approved rheumatic disease indication	Description	Mechanism of action	Usual dose range, route and frequency of administration	Pivotal Trials
infliximab Remicade[a] (1998)	RA[a], PSA[a], AS[a]	Chimeric	Inhibits TNFα	3-10 mg/kg IV infusion every 8 weeks after initial loading 5 mg/kg used for PSA, AS	ATTRACT[b], ASPIRE[c], IMPACT 1[d], IMPACT 2[e], Braun[f]
adalimumab Humira[a] (2002)	RA[a-c], PSA[a], AS[a]	Human	Inhibits TNFα	40 mg SC every other week, can increase to weekly	Van De Putte[g], ARMADA[h], PREMIER[i], ATLAS[j]
certolizumab Cimzia[a] (2008)	RA[a-c]	PEG-linked humanized Fab	Inhibits TNFα	200 SC mg every 2 weeks or 400 mg every 4 weeks after initial loading	RAPID 1[k], RAPID 2[l], FASTRAND[m]
golimumab Simponi[a] (2009)	RA[a], PSA[a], AS	Human	Inhibits TNFα	50 mg SC once monthly	GOBEFORE[n], GOFORWARD[o], GOAFTER[p], GOREVEAL[q], GORAISE[r]
tocilizumab Actemra[a] (2010)	RA[a-c]	Humanized	Inhibits IL-6	4-8 mg/kg IV infusion every 4 weeks	OPTION[s], TOWARD[t], RADATE[u], AMBITION[v]
rituximab Rituxan[a] (2006)	RA[a-c]	Chimeric	Depletes B cells	1000 mg IV infusion repeated 2 weeks later, then every 24 weeks[w,x]	DANCER[y], REFLEX[z]
canakinumab Ilaris[a] (2009)	CAPS	Human	Inhibits IL-1	150 mg SC every 8 weeks (adults and children ≥6 years old, >40 kg)	Lachmann[aa]
belimumab Benlysta[a] (2011)	SLE	Human	Inhibits BLYS	10 mg/kg every 2 weeks x 3, then every 4 weeks	BLISS 52[ab], BLISS 76[ac]

Farmaci steroidei

Profilassi antifungina a chi, quando e come???

- Vi è un reale aumento del rischio di PJP e altre infezioni fungine nei pazienti con malattia reumatologica?
- I farmaci reumatologici aumentano il rischio di infezioni fungine? Il rischio è dose/durata dipendente?
- Quali sono le infezioni fungine più frequenti?
- Dopo un'infezione fungina e nel caso in cui la terapia per la malattia reumatica non possa essere interrotta e/o modificata, è corretto continuare la terapia antifungina (dosi profilattiche?)

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EXTENDED REPORT

Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) Study

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ABSTRACT

Objectives To determine among patients with autoimmune diseases in the USA whether the risk of non-viral opportunistic infections (OI) was increased among new users of tumour necrosis factor α inhibitors (TNFI), when compared to users of non-biological agents used for active disease.

Methods We identified new users of TNFI among cohorts of rheumatoid arthritis (RA), inflammatory bowel disease and psoriasis-psoriatic arthritis-ankylosing spondylitis patients during 1998–2007 using combined data from Kaiser Permanente Northern California, two pharmaceutical assistance programmes for the elderly, Tennessee Medicaid and US Medicaid/Medicare programmes. We compared incidence of non-viral OI among new TNFI users and patients initiating non-biological disease-modifying antirheumatic drugs (DMARD) overall and within each disease cohort. Cox regression models were used to compare propensity-score and steroid- adjusted OI incidence between new TNFI and non-biological DMARD users.

Results Within a cohort of 33 324 new TNFI users we identified 80 non-viral OI, the most common of which was pneumocystosis (n=16). In the combined cohort, crude rates of non-viral OI among new users of TNFI compared to those initiating non-biological DMARD was 2.7 versus 1.7 per 1000-person-years (aHR 1.6, 95% CI 1.0 to 2.6). Baseline corticosteroid use was associated with non-viral OI (aHR 2.5, 95% CI 1.5 to 4.0). In the RA cohort, rates of non-viral OI among new users of infliximab were higher when compared to patients newly starting non-biological DMARD (aHR 2.6, 95% CI 1.2 to 5.6) or new etanercept users (aHR 2.9, 95% CI 1.5 to 5.4).

Conclusions In the USA, the rate of non-viral OI was higher among new users of TNFI with autoimmune diseases compared to non-biological DMARD users.

Negli USA, il tasso di IO non virali era maggiore tra le persone con malattia autoimmune che utilizzavano un inibitore TNF, rispetto a chi utilizzava un DMARD non biologico

Medication exposures

Claims data on pharmacy prescription fills and infusions were used to determine medication exposure following a new user design. Study DMARD were classified in two groups: TNFI (including infliximab, adalimumab and etanercept (not included for IBD)) and alternative non-biological DMARD regimens. For RA, alternative regimens were initiation of leflunomide, sulfasalazine or hydroxychloroquine after the use of methotrexate in the previous year (ie, methotrexate failures), whereas for IBD, the comparison group was initiation of azathioprine or 6-mercaptopurine (AZA/6-MP). For PsO-PsA-AS the comparison was initiation of non-biological DMARD (methotrexate, hydroxychloroquine, sulfasalazine and leflunomide).

Table 2 Distribution of non-viral OI (n=80) among new TNFI users for all disease indications*

Infection	Frequency (%)
Pneumocystosis	16 (20)
Nocardiosis/actinomycosis	12 (15)
tuberculosis	10 (12.5)
Histoplasmosis	9 (11.3)
Non-tuberculous mycobacteria	9 (11.3)
Salmonellosis	8 (10)
Listeriosis	4 (5)
Legionellosis	4 (5)
Cryptococcosis	3 (3.8)
Endemic fungal infection*	1 (1.3)
Toxoplasmosis	1 (1.3)
Coccidioidomycosis	1 (1.3)
Blastomycosis	1 (1.3)
Aspergillosis	1 (1.3)

*Only the first OI per patient is listed. One patient with tuberculosis was diagnosed with NTM several years later. That NTM case is not listed above but was used in analysis in table 5.
†Defined using ICD-9 484.7 (pneumonia in systemic mycoses). Not in table
NTM, non-tuberculous mycobacterial; OI, opportunistic infection, TNFI, tumour necrosis factor α inhibitor.

Rheumatoid arthritis

Compared with non-biological DMARD patients, the adjusted risk of non-viral OI in RA patients was not increased significantly among new users of any TNFI (aHR 1.6, 95% CI 0.9 to 3.1; table 3). Glucocorticoids had a borderline significant association with non-viral OI (aHR 1.8, 95% CI 1.0 to 2.8). There were differences among specific TNFI: infliximab (aHR 2.6, 95% CI 1.2 to 5.6) when compared with non-biological DMARD was associated with an increased risk of non-viral OI (table 4). In comparisons between specific TNFI, infliximab initiation was associated with an increased risk of non-viral OI when compared to etanercept (aHR 2.9, 95% CI 1.5 to 5.4).

In the mycobacterial analysis (table 5) most cases occurred in TNFI users with a crude rate four times greater for tuberculosis in this stratum, although the difference did not reach statistical significance (aHR 4.2, 95% CI 0.5 to 33.5). Rates of NTM were similar between exposure groups (table 5).

Una delle limitazioni: infezioni da Candida non incluse!

Table 2 – Incidence of infections during the 6 months after starting biological agents for rheumatoid arthritis treatment: post-marketing surveillance in Japan.

	Infliximab Ref. [3]	Adalimumab Ref. [4]	Etanercept Ref. [5]	Tocilizumab Ref. [6]	Abatacept information on proper use (Vol. 4)
No of patients	7522	7740	13,894	7901	3985
Smoking (current+ex-smoking)	ND	ND	ND	11.7	ND
Respiratory comorbidity	4.5%	13.4%	7.1%	26.1%	13.5%
Pneumonia	1.9%	1.3%	1.3%	1.5%	0.7%
Influenza	0.08%	0.18%	0.11%	0.13%	0.15%
Lung abscess	–	–	0.03%	0.01%	–
Empyema	–	0.03%	0.01%	0.05%	–
Tuberculosis	0.32%	0.1%	0.07%	0.05%	0.03%
NTM	0.11%	0.1%	0.12%	0.2%	0.05%
PCP	0.47%	0.34%	0.18%	0.2%	0.1%
Aspergillosis	–	0.03%	0.01%	0.01%	0.03%
Cryptococcosis	0.08%	0.04%	0.01%	–	–
Herpes zoster	1.09%	0.7%	0.81%	1.1%	0.98%

ND: no data, PCP: *Pneumocystis jirovecii* pneumonia, NTM: nontuberculous mycobacteriosis.

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Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

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Background Serious infections are a major concern for patients considering treatments for rheumatoid arthritis. Evidence is inconsistent as to whether biological drugs are associated with an increased risk of serious infection compared with traditional disease-modifying antirheumatic drugs (DMARDs). We did a systematic review and meta-analysis of serious infections in patients treated with biological drugs compared with those treated with traditional DMARDs.

Methods We did a systematic literature search with Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from their inception to Feb 11, 2014. Search terms included "biologics", "rheumatoid arthritis" and their synonyms. Trials were eligible for inclusion if they included any of the approved biological drugs and reported serious infections. We assessed the risk of bias with the Cochrane Risk of Bias Tool. We did a Bayesian network meta-analysis of published trials using a binomial likelihood model to assess the risk of serious infections in patients with rheumatoid arthritis who were treated with biological drugs, compared with those treated with traditional DMARDs. The odds ratio (OR) of serious infection was the primary measure of treatment effect and calculated 95% credible intervals using Markov Chain Monte Carlo methods.

Findings The systematic review identified 106 trials that reported serious infections and included patients with rheumatoid arthritis who received biological drugs. Compared with traditional DMARDs, standard-dose biological drugs (OR 1·31, 95% credible interval [CrI] 1·09–1·58) and high-dose biological drugs (1·90, 1·50–2·39) were associated with an increased risk of serious infections, although low-dose biological drugs (0·93, 0·65–1·33) were not. The risk was lower in patients who were methotrexate naive compared with traditional DMARD-experienced or anti-tumour necrosis factor biological drug-experienced patients. The absolute increase in the number of serious infections per 1000 patients treated each year ranged from six for standard-dose biological drugs to 55 for combination biological therapy, compared with traditional DMARDs.

Interpretation Standard-dose and high-dose biological drugs (with or without traditional DMARDs) are associated with an increase in serious infections in rheumatoid arthritis compared with traditional DMARDs, although low-dose biological drugs are not. Clinicians should discuss the balance between benefit and harm with the individual patient before starting biological treatment for rheumatoid arthritis.

Lancet 2015; 386: 258-65

Serious infection during etanercept, infliximab and adalimumab therapy for rheumatoid arthritis: A literature review

The purpose of this review is to establish whether there is a significantly increased incidence of serious infections during treatment for rheumatoid arthritis (RA) with etanercept, infliximab or adalimumab, to determine the background risk of serious infection in RA patients without treatment with any biological therapy and to ascertain which organisms are involved in serious infections in RA patients while being treated with etanercept, infliximab or adalimumab. Randomised controlled trials (RCTs), meta-analyses of RCTs, Cochrane reviews, national registry articles and case reports were identified using PubMed/MEDLINE, The Cochrane Library and Google Scholar. The medical subject heading "rheumatoid arthritis" was combined with "serious infection" or "infection" or "adverse drug events" with each of the three reference biological therapies separately: etanercept, infliximab and adalimumab. These electronic searches were limited to human studies, adult studies, those published in the last 10 years (2004–14) and in the English language. Studies which involved the tumor necrosis factor-α inhibitors certolizumab pegol or golimumab were excluded. The background risk of serious infection appears to be approximately two-fold more than non-RA patients before any treatment with biological therapy. The national registries, which may represent the typical RA patient more accurately than clinical trials, suggest a small but significantly increased incidence of serious infection ranging 1.2–2.78 times that of control (treatment with methotrexate). *Mycobacteria* spp., *Staphyloccus aureus*, *Listeria monocytogenes*, Varicella zoster virus and Leishmania species (spp.) repeatedly appear in the case report literature and should be in the mind of the clinician faced with a serious infection in a RA patient with an unknown pathogen who is being treated with either etanercept, infliximab or adalimumab.

Colum DOWNEY

International Journal of Rheumatic Diseases 2015

Rituximab-Associated Infections

Table 1. Rituximab Infectious Complications

	Evidence	Comments
Established increased infectious complications		
Overall infections	Meta-analyses in hematologic malignancies[11,12] Randomized trials in RA[1]	Increased severe infections (grade 3 or 4) when used as maintenance therapy in follicular lymphoma Mild infections in RA
Hepatitis B reactivation	Case series[13–15] Case reports[16–18]	Reports only in hematologic malignancies
PML	Case series,[19] case reports[20–22]	Most cases in hematologic malignancies, but a few in RA, SLE, and immune cytopenia
Possibly increased infectious complications		
Pneumocystis jirovecii pneumonia	Retrospective series compared to historical controls[23,24] Case series[25–27] Case reports[28–31]	Cases in hematological malignancies, RA, autoimmune diseases, solid organ transplant
Enterovirus encephalitis	Case reports[32–35]	Known complication of other B-cell immunodeficiencies
Parvovirus B19	Case reports[36–39]	Good response to IVIG
Cytomegalovirus	Case reports[20,28,40]	CMV disease is very uncommon except in HIV or following allogeneic transplant; there are several reports in hematologic malignancies treated with combination chemotherapy
West Nile virus	Case reports[41,42]	Increased severity and negative serology may be anticipated because of effect of rituximab on B cells
Babesiosis	Case-control study[43]	Most patients with persistent babesiosis had received rituximab
Mycobacterial disease	Case reports[44]	Severe *Mycobacterium avium* and *M kansasii*, no other reports

Gea-Banacloche *Seminars in Hematology*, Vol 47, No 2, April 2010, pp 187–198

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Analysis of Underlying Diseases and Prognosis Factors Associated with *Pneumocystis carinii* Pneumonia in Immunocompromised HIV-Negative Patients

Published online: 13 July 2002
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Fattori associati alla PJP
in pazienti non-HIV.

Table 1 Underlying diseases at diagnosis of *Pneumocystis carinii* pneumonia

Underlying disease or condition	No. of patients[a]
Hematologic malignancy (n=60)	
Myelodysplasia	4
Non-Hodgkin's disease	15
Hodgkin's disease	2
Chronic lymphocytic leukemia	13
Multiple myeloma	5
Waldenström disease	4
Acute leukemia	12
Miscellaneous	5
Inflammatory and autoimmune disease (n=27)	
Rheumatoid arthritis	6
Inflammatory bowel disease	2
Vasculitis	3
Lupus	1
Idiopathic pulmonary fibrosis	2
Miscellaneous[b]	13
Transplantation (n=24)	
Bone marrow	15
Heart	1
Liver	4
Kidney	4
Solid tumor[c] (n=18)	
Idiopathic CD4+ lymphopenia (n=1)	

Pneumocystis jirovecii

•PJP (polmonite da Pneumocistys jirovecii) descritta negli anni ’60 in pazienti con artrite reumatoide, oltre che in altri “ospiti”, ampiamente studiata con l’esordio dell’epidemia dell’HIV.
•Da allora maggior riscontro in altre connettiviti

Considerati a rischio:

•HIV-infected patients with a low CD4 count
•Hematopoietic stem cell and solid organ transplant recipients
•Patients with cancer (particularly hematologic malignancies),
•and those receiving glucocorticoids, chemotherapeutic agents, and other immunosuppressive medications.

Editorial

Is There a Role for Consensus Guidelines for *P. jiroveci* Pneumonia Prophylaxis in Immunosuppressed Patients with Rheumatic Diseases?

The Journal of Rheumatology 2010; 37:4

Pneumocystis jiroveci pneumonia (PCP) is the most common opportunistic infection in patients with human immunodeficiency virus (HIV)[1]. PCP can also affect patients with autoimmune diseases [e.g., systemic lupus erythematosus (SLE), Wegener's granulomatosis (WG), rheumatoid arthritis (RA), and inflammatory bowel disease] as well as hematological malignancies, organ transplants, and those receiving longterm immunosuppression. In the HIV population, the significant morbidity and mortality of PCP led to the development of specific guidelines for prevention, which has resulted in a dramatic reduction in the incidence of PCP. Similar guidelines for PCP prophylaxis have been developed for patients with organ transplants and undergoing cancer treatment[2,3].

Le linee-guida sulla profilassi della PJP nei pazienti con infezione da HIV ha significativamente diminuito la morbidità e la mortalita; linee guida sono state create per pazienti trapiantati e con alcuni tumori.

Perché non esistono linee guida per profilassi in pazienti con malattia reumatica?

Sepkowitz KA. Clin Infect Dis 2002.

Approximately 1 to 2 percent of patients with rheumatologic diseases develop PJP, usually in the setting of immunosuppressive therapy, particularly combined therapy

Table 1. Incidence, clinical presentation, outcome, and prevention of *Pneumocystis carinii* pneumonia (PCP) among patients who did not receive prophylaxis and did or did not have HIV infection.

	Patient group, by disease or condition				
Variable	AIDS	Cancer[a]	Transplantation[a]	CVD	Other
Incidence	>50% [4]	Varies by type of cancer [5]; 22%–45% for ALL [6] and NHL [5], >25% for SCID [5], 25% for rhabdomyosarcoma [5], 1.3% for solid tumor while receiving CS [7]	5%–10% for all [5, 8–10]; >25% for lung transplant recipients [11, 12]	<2% for all types [13]; >6% for Wegener's granulomatosis [13, 14]	No data available; reports in the early 1990s described PCP without underlying immunodeficiency [15, 16]
Clinical presentation [17, 18]					
Prodrome duration, days	28	<5	<5	<5	NA
Pa_{O_2}, mm	69	50	50	NA	NA
Parasite load	Many	Few	Few	Few	Few
Outcome: survival rate	>80%	50% [5]	90% of kidney transplant recipients [19]	68% [13]	NA
Preventive measures[b]	Patients with CD4 counts of <200 cells/mm³ [2] or a history of thrush [2]	>20 mg of a prednisone equivalent for >1 month [5]	Allo BMT recipients: during months 2–6, longer if there is chronic GVHD [3]; auto BMT recipients: consider for patients with intense conditioning or recent use of fludarabine, Campath antibodies, or a similar compound [3]; SOT recipients: during the period of maximal immunosuppression [20, 21]	NR	NR

NOTE. ALL, acute lymphocytic leukemia; allo, allogeneic; auto; autologous; CS, glucocorticosteroids; CVD, collagen vascular disease; GVHD; graft-versus-host disease; NA, no data available; NHL, non-Hodgkin's lymphoma; NR, no recommendation; Pa_{O_2}, partial pressure of oxygen; SCID, severe combined immune deficiency; SOT, solid-organ transplant.

[a] Rate related to intensity of chemotherapy or immunosuppressive therapy used (see the section on PCP in the text).

[b] Preventive measures recommended for the at-risk patients who meet the criterion or criteria specified.

It is not clear if there is a specific propensity to develop PJP in certain rheumatic diseases.

Some rheumatologists feel that the risk may be greater in polymyositis/dermatomyositis and lower in systemic lupus erythematosus (SLE) at the same intensity of immunosuppression

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Studio retrospettivo di 5 anni che aveva lo scopo di determinare stati clinici associati alla PJP, (in pazienti senza infezione da HIV) e identificare i fattori prognostici.

LDH e PCR elevati
FR elevata
FC elevata
Ventilazione meccanica

Perché peggior outcome nei pazienti senza infezione da HIV?

Limper and colleagues investigated a possible pathophysiologic basis for the differences in presentation and outcome. They examined the numbers of *P. carinii parasites and* the lung inflammatory cell populations in bronchoalveolar lavage specimens obtained from patients with and patients without AIDS. The investigators found that patients with AIDS had significantly higher numbers of *P. carinii and substantially fewer* neutrophils in the lavage fluid samples than did other immunocompromised patients with PCP. They hypothesized that the number of neutrophils negatively influenced overall survival, concluding that lung inflammation contributed to respiratory impairment in patients with PCP. According to this hypothesis, HIV-negative patients with PCP have higher rates of complication and death, paradoxically, because they have a superior capacity for inflammation. Alternatively, other more complex and less conspicuous factors may account for the difference.

Differenza nel BAL

Sepkowitz KA. Clin Infect Dis 2002.

Editorial

Is There a Role for Consensus Guidelines for *P. jiroveci* Pneumonia Prophylaxis in Immunosuppressed Patients with Rheumatic Diseases?

The Journal of Rheumatology 2010; 37:4

The goal of remission in rheumatic diseases has led to widespread use of intensive immunosuppressive regimens. Commonly used immunosuppressive therapies have been associated with PCP including cyclophosphamide, methotrexate (MTX), corticosteroids, azathioprine, cyclosporine, and the newer biological agents including anti-tumor necrosis factor and anti-CD20 agents. Corticosteroids seem to be an important risk factor, with up to 90% of patients receiving corticosteroid therapy prior to development of PCP[7]. Cyclophosphamide can be associated with prolonged and significant reduction in lymphocyte counts; whether monitoring CD4+ lymphocyte counts should become routine clinical practice will be considered below. There is debate as to the extent of risk associated with MTX, but at least in RA the risk of infections is lower than has been thought in the past[8].

Maggior remissione delle patologie reumatiche

↓

Incremento regimi immunosoppressivi

↓

Aumento infezioni opportunistiche tra cui PJP

Noto da anni l'associazione dell'uso di corticosteroidi con PJP

Studio retrospettivo del 1996, su 116 pazienti con PJP (non HIV): il 90.5% aveva assunto terapia con corticosteroidi nel mese precedente l'esordio, per la malattia di base

In a case series from the Mayo Clinic of 116 consecutive HIV-uninfected patients with a first episode of PCP, glucocorticoids had been administered within one month of diagnosis in 91 percent . **The median dose of prednisone equivalent in these patients was 30 mg/day, but some patients received as little as 16 mg/day.** The median duration of glucocorticoid therapy before the development of PCP was 12 weeks, **but 25 percent of patients had been receiving glucocorticoids for ≤8 weeks.** Concurrent use of other immunosuppressive drugs was not reported. The following underlying diseases were present:

- Hematologic malignancy – 30 percent
- Organ transplantation – 25 percent
- Inflammatory conditions, such as granulomatosis with polyangiitis (Wegener's) and polymyositis/dermatomyositis – 22 percent
- Solid tumors – 13 percent
- Other miscellaneous conditions – 10 percent

Mayo Clin Proc. 1996 jan; 71(1): 5-13.

POSSIBILE MECCANISMO DEI GLUCOCORTICOIDI NEL PREDISPORRE ALLA PJP

Soppressione dell'immunità cellulo-mediata e alterazione del surfactante nel polmone.
L'uso di GC in assenza di altri forme di immunosoppressione (ad esempio paziente con asma) non è sufficiente a causare un rischio di PJP, anche se…

Editorial

Is There a Role for Consensus Guidelines for *P. jiroveci* Pneumonia Prophylaxis in Immunosuppressed Patients with Rheumatic Diseases?

The Journal of Rheumatology 2010; 37:4

Morbidity and Mortality Associated with PCP in Rheumatic Diseases

PCP in patients with rheumatic diseases is associated with significant morbidity and mortality. The need for intensive care admission and assisted ventilation is high. The overall mortality from PCP in HIV-negative patients is ~30%–60%, significantly higher than the reported 10%–20% mortality rate in HIV-positive patients.

The estimated mortality from PCP in patients with underlying rheumatic disease varies according to the condition; 62.5% in WG, 57.7% in inflammatory myopathy, 47.6% in polyarteritis nodosa, 30.8% in RA, and 16.7% in systemic sclerosis.

Considerando la maggior mortalità per PJP nei pazienti HIV-negativi, quale potrebbe essere la soglia dei ly CD4+?

Guidelines have been published for the use of *Pneumocystis* pneumonia (PCP) prophylaxis in patients with cancer, including hematopoietic stem cell transplant (HCT) recipients **[20-22],** as well as in solid organ transplant **recipients [23].** There are no published guidelines for PCP prophylaxis among patients with rheumatologic diseases receiving immunosuppressive drugs, but some advocate its use in such patients when they are receiving high-dose immunosuppressive therapy

Individuals with the following risk factors should receive PCP prophylaxis based upon the evidence for substantial risk of PCP:

- Patients receiving a glucocorticoid dose equivalent to ≥20 mg of prednisone daily for one month or longer who also have another cause of immunocompromise (eg, certain hematologic malignancies or a second immunosuppressive drug) [1,15,20,27-29]

Stern A, Green H, Paul M, et al. ***Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients****. Cochrane Database Syst Rev 2014;*

Combinazioni di farmaci immunosoppressori

Some authorities recommend PCP prophylaxis for patients receiving certain combinations of immunosuppressive drugs.

TNFI
+
GC o altri farmaci immunosoppressori

Among patients with rheumatologic diseases, prophylaxis is usually given to those who are treated with significant doses of glucocorticoids (eg, ≥20 mg of prednisone daily for one month or longer) in combination with a second immunosuppressive drug, particularly a cytotoxic agent (eg, cyclophosphamide), as is commonly used in granulomatosis with polyangiitis (Wegener's).

Prednisone
+
ciclofosfamide

Secondo alcuni autori, profilassi:

SI, in pazienti con granulomatosi con poliangioite (Wegener), in terapia con MTX + alte dosi di corticosteroidi

NO in pazienti con artrite reumatoide trattati con MTX con o senza corticosteroidi a basse dosi.

Profilassi anti PJ nei pazienti reumatologici??

- Prednisone ≥20 mg/d per ≥1 mese
- Azatioprina + Ciclofosfamide
- Ciclofosfamide + CS
- Inibitori del TNF ± CS?

Suryaprasad, Arthritis Rheum 2008; Stern, Cochrane Database Syst Rev 2014; Grubbs, Curr Rheumatol Rep 2014

MAJOR ARTICLE

Biologic Therapies in Rheumatoid Arthritis and the Risk of Opportunistic Infections: A Meta-analysis

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Objective. Biologic agents are increasingly used to treat patients with rheumatoid arthritis (RA). We aimed to review their association with opportunistic infections (OIs), including fungal, viral (with a focus on herpesvirus-related infections), tuberculosis and other mycobacterial infections.

Methods. We searched PubMed and EMBASE through June 24, 2013, and complemented the search with the reference lists of eligible articles. The analysis included randomized trials on RA that compared any approved biologic agent with controls and reported the risk of OIs.

Results. A total of 70 trials that included 32 504 patients (21 916 patients receiving biologic agents and 10 588 receiving placebo) were deemed eligible. Biologic agents increased the risk of OIs (pooled Peto odds ratio [OR], 1.79; 95% confidence interval [CI], 1.17–2.74; $I^2 = 3\%$), resulting in 1.7 excess infections per 1000 patients treated (number needed to harm, 582). A significant risk was noted for mycobacterial (OR, 3.73; 95% CI, 1.72–8.13; $I^2 = 0$), and viral (OR, 1.91; 95% CI, 1.02–3.58; $I^2 = 0$) infections. Interestingly, no significant differences were found for invasive and superficial fungal infections (1.31; 95% CI, .46–3.72), invasive fungal infections (2.85; .68–11.91), *P. jirovecii* pneumonia (1.77; .42–7.47), varicella-zoster virus (1.51; .71–3.22), as well as overall mortality attributed to OIs (1.91; .29–12.64).

Conclusions. Among patients with RA, biologic agents are associated with a small but significant risk of specific OIs. This increase is associated with mycobacterial diseases and does not seem to affect overall mortality. Because OIs are a relatively rare complication of biologic agents, large registries are needed to identify the exact effect in different OIs and to compare the different biologic agents.

Keywords. opportunistic; infections; rheumatoid arthritis; biologic; meta-analysis.

In conclusion, biologic agents are safe medications for the treatment of RA when it comes to the development of OIs, which are rare events, and the use of these agents does not seem to affect the overall mortality rate associated with OIs. Overall, patients receiving biologic agents seem more likely to develop OIs than control patients, and the use of biologic agents is associated with increased risk of mycobacterial and viral OIs; for fungal infections, *P. jirovecii* pneumonia, and VZV infections, the differences did not reach statistical significance. Large registries are needed to monitor and further investigate the trends for these rare complications.

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Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis

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Importanza del Rischio individuale, dei fattori non modificabili e di quelli modificabili.
Quale score?
Maggior rischio per pazienti che cambiano terapia (ma in genere malattia attiva e uso di steroidi ad alte dosi).

Summary and conclusions

The number of biological agents available for the treatment of RA has increased exponentially in recent years. Although the agents are effective, there is also a small but significant increased risk of SI. Anti-TNF drugs are the most well studied, with an early increased risk of SI compared with sDMARD – a finding seen in both clinical trials and observational studies. There is a slightly higher rate of SI with infliximab. The risk of SI with the newer biologics may be comparable, though data from long-term observational studies are awaited. There is an increased risk of TB with anti-TNF, especially infliximab, with very high rates observed for the newer anti-TNF therapies albeit in settings with high background rates of infection. The risk of TB is declining over time, thus signalling that screening and prophylaxis strategies are effective, at least in countries with low TB prevalence. The risk of HZ is increased with tofacitinib. Overall, the risk of SI is largely determined by both modifiable and non-modifiable patient characteristics such as age, co-morbidity, GC use and functional status. It is now possible to risk-stratify patients using risk scores prior to starting these expensive therapies.

STRATEGIA: CALCOLARE IL RISCHIO INDIVIDUALE PRIMA DI INIZIARE UNA TERAPIA BIOLOGICA

Curr Rheumatol Rep (2014) 16:445
DOI 10.1007/s11926-014-0445-4

INFECTIONS AND ARTHRITIS (K WINTHROP, SECTION EDITOR)

Pneumocystis jirovecii Pneumonia in Patients Receiving Tumor-Necrosis-Factor-Inhibitor Therapy: Implications for Chemoprophylaxis

James A. Grubbs · John W. Baddley

Table 1 Agents for the treatment and/or prophylaxis of PJP

Medication	Dosing	Adverse effects
TMP–SMX, treatment	15–20 mg TMP kg^{-1} day^{-1}, divided q6 or 8 h ×21 days	Rash, leukopenia, thrombocytopenia
TMP–SMX, prophylaxis	160 mg TMP daily or three times weekly	As above
Dapsone and trimethoprim, treatment	100 mg daily with TMP 15–20 mg kg^{-1} day^{-1}, divided q6 or 8 h ×21 days	Cytopenia, hemolysis (particularly with G6PD deficiency), methemoglobinemia, rash, pancreatitis, hepatitis, mononucleosis-like illness
Dapsone, prophylaxis	100 mg daily or 50 mg daily with pyrimethamine 50 mg and leucovorin 25 mg weekly	As above
Pentamidine IV, treatment	4 mg kg^{-1} daily ×21 days	Kidney injury (29 %), hypotension (5 %), confusion and/or hallucinations (2 %), hypoglycemia (6 %), leukopenia (10 %)
Pentamidine inhaled, prophylaxis	300 mg every 4 weeks	Fatigue (66 %), fever (51 %)
Atovaquone, treatment	750 mg twice daily with food ×21 days	Fever, headache, rash, diarrhea, nausea, hyponatremia, amylase increased
Atovaquone, prophylaxis	1500 mg daily with food	As above
Clindamycin and primaquine, treatment	600–900 mg q6–8 h IV or 300–450 mg q6 h oral and 30 mg daily, respectively, × 21 days	Clindamycin: rash, abdominal pain, diarrhea, LFT abnormalities Primaquine: hemolytic anemia (with G6PD), leukopenia, methemoglobinemia, nausea, vomiting

Table 2 Studies on the incidence of PJP among patients on TNFi

Reference	Study type	Location and time	Follow-up (person-years)	Incidence of pneumocystis (cases per 1000 person-years)
Lichtenstein GR, et al. [69]	Prospective cohort	North America, 1999–2010	17,712	<0.01 (1 case)
Baddley JW, et al. [70••]	Retrospective cohort	United States, 1998–2007	28,493	0.56
Dixon WG, et al. [71]	Prospective cohort	Great Britain, 2001–2005	9,868	0
Greenberg JD, et al. [72]	Prospective cohort	United States, 2001–2006	15,047	0.14
Salmon-Ceron D, et al. [73••]	Prospective cohort	France, 2004–2007	57,711	0.087
Takeuchi T, et al. [74]	Prospective cohort	Japan, 2003–2004	2,500	8.8
Koike T, et al. [75]	Prospective cohort	Japan, 2005–2006	3,272	4.6
Komano Y, et al. [76]	Prospective cohort	Japan, 2003–2008	582	5
Beukelman T, et al. [77]	Retrospective cohort	United States, 2000–2005	1,765	0.07

L'uso di corticosteroidi è il principale fattore di rischio per la PJP nei pazienti senza infezione da HIV. I pazienti che assumono farmaci immunomodulanti inclusi gli inibitori del TNF, sono a rischio di PJP, ma non vi sono sufficienti studi per fornire specifiche indicazioni sulla profilassi.

DIAGNOSI DIAGNOSI DIAGNOSI

SOSPETTO CLINICO ANCHE SE QUADRO RADIOLOGICO NON E' SIGNIFICATIVO!

SPESSO NECESSARIO ESECUZIONE TC TORACE

LDH,
PCR,…

EGA

- PCR su BAL o (espettorato indotto); sensibile ma difficile discriminare dalla colonizzazione
- β-D-glucano

Infezioni da *Candida*

Immunocompromised patients are at special risk for candidemia.

High-risk groups include:

- Those with hematologic malignancies
- Recipients of solid organ or hematopoietic stem cell transplants
- Those given chemotherapeutic agents, especially those associated with extensive gastrointestinal mucosal damage

Fattori di Rischio in pazienti in Terapia Intensiva

- CVC
- Nutrizione parenterale
- Antibiotici ad ampio spettro
- Alto APACHE score
- IRA
- Perforazione tratto gastro-intestinale, chirurgia addominale

PLOS | ONE

RESEARCH ARTICLE

Long-Term Trends in Esophageal Candidiasis Prevalence and Associated Risk Factors with or without HIV Infection: Lessons from an Endoscopic Study of 80,219 Patients

Yuta Takahashi[1], Naoyoshi Nagata[1]*, Takuro Shimbo[2], Takeshi Nishijima[3], Koji Watanabe[3], Tomonori Aoki[1], Katsunori Sekine[1], Hidetaka Okubo[1], Kazuhiro Watanabe[3], Toshiyuki Sakurai[1], Chizu Yokoi[1], Masao Kobayakawa[1], Hirohisa Yazaki[3], Katsuji Teruya[3], Hiroyuki Gatanaga[3], Yoshimi Kikuchi[3], Sohtaro Mine[4], Toru Igari[4], Yuko Takahashi[5], Akio Mimori[5], Shinichi Oka[3], Junichi Akiyama[1], Naomi Uemura[6]

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OPEN ACCESS

Citation: Takahashi Y, Nagata N, Shimbo T, Nishijima

80.219 pazienti sottoposti a EGDS tra il 2002 e il 2014. CE studiata su 6011 pazienti.
Primo studio per studiare la prevalenza delle CE
Il secondo studio per esaminare i fattori di rischio.

FATTORI INDIPENDENTEMENTE ASSOCIATI ALLE CE

Conclusions
This large, endoscopy-based study demonstrated that CE prevalence increased in non-HIV-infected patients but decreased in HIV-infected patients over 13 years. Risk analysis revealed that increasing age, HIV infection, and corticosteroids use, particularly at higher doses, were independently associated with CE, but alcohol, other infections, diabetes, anticancer drugs, and PPIs use were not.

SI: HIV e corticosteroidi

NO: Alcool, diabete, altre infezioni, PPI e chemioterapici

Br J Dermatol. 2016 Aug 31. doi: 10.1111/bjd.15015. [Epub ahead of print]

Candida infections in psoriasis and psoriatic arthritis patients treated with IL-17 inhibitors and their practical management.

Saunte DM[1], Mrowietz U[2], Puig L[3], Zachariae C[4].

Author information

Abstract

The recognition of the central role of interleukin 17A (IL-17A) in the pathogenesis of psoriasis has led to the development of several monoclonal antibodies targeting this cytokine or its receptors for therapeutic purposes. IL-17A also plays an important role in the immunological protection against infections, especially those due to Candida sp., as evidenced by findings in patients with genetic defects in IL-17 related immune responses. To assess the potential of anti-Il-17 treatment to promote Candida infections, here we have systematically reviewed published clinical trials of patients with psoriasis or psoriatic arthritis. Candida infections were reported in 4.0% of patients treated with brodalumab, 2.1% with secukinumab, and 3.3% with ixekizumab, compared with 0.3%, 2.3% and 0.8% of those assigned to placebo, ustekinumab or etanercept, respectively. Although the incidence of Candida infection was found to be increased by a only small degree during anti-IL-17 therapy, patients undergoing such treatment should be monitored for fungal infection and treated as necessary. We propose to adopt the recently updated recommendations for the practical management of Candida infection in patients administered with IL-17 inhibitors. This article is protected by copyright. All rights reserved.

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KEYWORDS: anti- IL17; brodalumab; candida; candidiasis; ixekizumab; psoriasis; psoriatic arthritis; secukinumab

RUOLO DELL'IL-17

ASPERGILLOSI INVASIVA

- Cellule epiteliali vie respiratorie
- Macrofagi alveolari

Inhaled conidia are met by the innate defenses provided by resident phagocytes, specifically airway epithelial cells and alveolar macrophages [1,2]. Little is known about the contribution of epithelial cells in clearing conidia. Relatively more is known about macrophages, which contribute to both conidial clearance and the production of secondary inflammation. These cells secrete inflammatory mediators after recognition of key cell wall components (eg, beta-D-glucan) exposed after conidial germination into hyphal forms. These mediators result in neutrophil recruitment and the activation of cellular immunity, which are important in killing potentially invasive microbial forms (hyphae) and determining the extent and nature of the immune response. Hence, risks for disease and the type of disease that occurs are the combined result of multiple cellular functions that impact proximal events in conidial clearance, production of inflammation, and killing of invasive forms [1].

RISK FACTORS — Underlying conditions that compromise pulmonary and systemic immune responses to inhaled *Aspergillus* species serve as risk factors for invasive pulmonary aspergillosis.

Classic risk factors include:

- Severe and prolonged neutropenia
- Receipt of high doses of glucocorticoids
- Other drugs or conditions that lead to chronically impaired cellular immune responses (eg, immunosuppressive regimens administered to treat autoimmune diseases and to prevent organ rejection, AIDS)

Quando sospettare IPA (aspergillosi polmonare invasiva)?

Table 1
Risk factors for IPA.

Recent history of severe neutropenia (<500/microl for >10 days)
Allogeneic stem cell transplant
Prolonged steroid use (>0.3 mg/kg/day prednisone equivalent > 3 weeks)
T-cell immunosuppressant treatment during the previous 3 months (e.g. cyclosporine, TNF-alpha blockers, specific monoclonal antibodies, or nucleoside analogues)
Inherited severe immunodeficiency
"Additional risk factors"
Chronic obstructive pulmonary disease (COPD)
Acquired immunodeficiency syndrome (ARDS)
Solid-organ transplant (SOT) recipient
Decompensated liver disease
Severe alcoholic hepatitis
Critically ill patients with severe sepsis
H1N1 critically ill patients
Critically ill patients with ECMO support
"Environmental risk factors"
Fungal contamination of indoor air: construction or demolition works in the hospital or its environment

Koulenti D, Garnacho-Montero J, Blot S. Approach to invasive pulmonary aspergillosis in critically ill patients. Current opinion inf dis 2014;27(2). 174–183.

BMJ Case Rep. 2014 Nov 14;2014. pii: bcr2014207335. doi: 10.1136/bcr-2014-207335.

Pulmonary co-infection with Nocardia and Aspergillus in a patient with adult-onset Still's disease receiving steroids and tacrolimus.

Misra DP[1], Parida JR[1], Chowdhury AC[1], Agarwal V[1].

Author information

Abstract

Patients on immunosuppression are at risk of unusual infections. We present a man diagnosed to have adult-onset Still's disease who, on high-dose oral steroid and tacrolimus, developed a cavitating pneumonia due to co-infection with Aspergillus flavus and Nocardia. Timely diagnosis and institution of appropriate therapy resulted in a favourable clinical outcome. Such co-infection in a patient receiving tacrolimus is rare in the published literature. This case serves to emphasise the need to be vigilant for unusual infections in patients who are immunosuppressed, either due to drugs or underlying disease condition.

J Neurol Surg A Cent Eur Neurosurg. 2015 May;76(3):249-54. doi: 10.1055/s-0034-1372435. Epub 2014 Jul 21.

Rapidly Fatal Internal Carotid Artery Mycotic Aneurysm Rupture in a Rheumatoid Patient Taking a TNF-α Inhibitor: Case Report and Literature Review.

Bowers CA[1], Saad D[2], Clegg DO[2], Ng P[3], Clayton F[4], Haydoura S[5], Schmidt RH[1].

Mucormicosi

Corticosteroid Use and Rheumatic Diseases.
Chronic corticosteroid-based therapy is another primary risk factor that enhances a patient's susceptibility to mucormycosis by causing defects in macrophages and neutrophils and/or steroid-induced diabetes [3]. In the few cases of mucormycosis in patients with systemic lupus erythematosus reported in the English-language literature [77–91], the infection apparently could present in any clinical form, but disseminated mucormycosis was common and the mortality rate was very high (88%) [78]. Additional predisposing factors for opportunistic mucormycosis include hypocomplementemia, nephrotic syndrome, uremia, leukopenia, and diabetes mellitus. Opportunistic mucormycosis occasionally occurs in patients with other autoimmune diseases.

Criptococco

Principale fattore di rischio associato è l'uso di corticosteroidi, qualunque sia l'indicazione! Non dati disponibili e statisticamente significativi su altri farmaci.

Grazie…