

# Incidence of Malignancies in a Cohort of Psoriatic Arthritis Patients Taking Traditional Disease Modifying Antirheumatic Drug and Tumor Necrosis Factor Inhibitor Therapy: An Observational Study

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**ABSTRACT. Objective.** Psoriatic arthritis (PsA) is an inflammatory arthropathy, associated with skin and/or nail psoriasis. As suggested in 2012 by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), studies devoted to assess cancer in the PsA population are still limited and need to be increased. Therefore, the aim of this study was to determine the incidence of malignancies in patients with PsA who are taking conventional and biologic therapies.

**Methods.** A cohort of patients with PsA was followed prospectively. At first visit, as well as at each 3–4 month followup visit, according to standardized clinical practice, medical history, and physical and laboratory findings were recorded. Information on the presence of comorbidities, as well as malignancies, was collected. At each visit, data were recorded on radiography and pathology, confirming malignancy diagnosis, when present.

**Results.** A total of 618 patients with PsA were included in the study. In particular, 296 were taking anti-tumor necrosis factor- $\alpha$  (anti-TNF) agents and 322 were taking disease-modifying antirheumatic drugs (DMARD). During the observation period, in the total group, 44 patients (7.1%) had a diagnosis of malignancy. Of them, 14 (4.7%; 95% CI 2.8–7.8; 0.52/100 patient-yrs) received anti-TNF therapy and 30 (9.3%; 95% CI 6.6–13.0; 1.03/100 patient-yrs) received traditional DMARD ( $p = 0.019$ ). However, after adjusting for major demographic and clinical characteristics, the difference between the 2 treatments was no longer significant ( $p = 0.480$ ), and the only predictor of malignancy occurrence was age (HR 1.04, 95% CI 1.009–1.073,  $p = 0.012$ ).

**Conclusion.** Data from this study confirm that biological therapies do not lead to any increased risk for cancer development, when adequately administered and with proper followup. (First Release September 15 2016; J Rheumatol 2016;43:2149–54; doi:10.3899/jrheum.160542)

**Key Indexing Terms:**  
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MALIGNANCIES  
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Psoriatic arthritis (PsA) is an inflammatory arthropathy, associated with skin and/or nail psoriasis and other possible systemic features, including uveitis and inflammatory bowel disease<sup>1,2,3,4,5,6</sup>. Several classification criteria have been used and among them, the CASPAR (ClASsification for Psoriatic ARthritis) Criteria have the wider consensus, because of high specificity and sensitivity<sup>7,8</sup>.

Prior to the introduction of biological agents, the treatment of PsA included different therapies from initial treatment with nonsteroidal antiinflammatory drugs to one or more synthetic disease-modifying antirheumatic drugs (DMARD) for the suppression of inflammation in patients with peripheral joint involvement. In clinical practice, the most widely used synthetic DMARD are methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), and cyclosporine (CSA)<sup>9</sup>.

Improved understanding of the molecular mechanisms

involved in PsA has opened up new and interesting therapeutic scenarios<sup>10,11,12,13,14</sup>. The use of the tumor necrosis factor (TNF)- $\alpha$  blockers infliximab (IFX), etanercept (ETN), adalimumab (ADA), golimumab (GOL), and certolizumab has improved PsA outcomes<sup>15</sup>.

To date, data on safety both of traditional DMARD and anti-TNF therapy in patients with PsA have been derived mainly from randomized clinical trials, but these do not provide sufficient information on longterm incidence of possible comorbidities, mainly of an oncologic nature, and do not fully reflect real-world practice<sup>16</sup>.

On the other hand, studies in the clinical setting show many difficulties in establishing definitely whether oncologic comorbidities are connected to immune-inflammatory psoriatic mechanisms or can be influenced by the effect of immunosuppressive and biologic therapies<sup>17</sup>.

Some studies have suggested that the survival of patients with psoriasis and PsA, independent of use of DMARD or TNF blockers, was not significantly different from the general population<sup>18,19,20</sup>. In 2008, Rohekar, *et al* assessed malignancy rates in over 660 patients with PsA, showing that the incidence of malignancy in that large PsA cohort did not differ from that in the general population<sup>19</sup>. Importantly, not many patients were receiving anti-TNF agents at the time.

On the other hand, some studies have shown that patients with psoriatic disease and those with PsA had an increased risk of malignancies, in particular lung, lymphoproliferative, and skin malignancies<sup>21,22,23,24,25,26,27,28</sup>. The risk of oncologic diseases, especially the occurrence of skin cancer, described in patients with psoriatic diseases who were taking DMARD (MTX and CSA), has been in part considered related to psoralen ultraviolet A (PUVA) exposure<sup>26,28,29</sup>.

Data on oncologic comorbidities in patients taking anti-TNF agents have been investigated mainly in extended metaanalyses that confirm the safety of these therapies<sup>30,31</sup>. In 2013, Haynes *et al* compared the incidence of cancer in patients taking TNF inhibitor therapy to that of patients taking commonly used alternative therapies in the context of different multiple immune-mediated diseases, including psoriasis and PsA<sup>20</sup>. The study showed that in patients taking anti-TNF therapy, the short-term cancer risk was not elevated. In particular, in more than 1300 patients with psoriatic disease (371 person-yr), and 2500 patients with PsA (618 person-yr), the incidence of any solid cancer was not elevated during biologic therapy as compared to disease-specific alternative treatment.

However, as suggested in 2012 by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), studies devoted to assess cancer in the PsA population are still limited and need to be increased<sup>17</sup>.

Therefore, the aim of our study was to determine the incidence of malignancies in patients with PsA taking conventional and biologic therapies.

## MATERIALS AND METHODS

A cohort of 618 patients with PsA was followed prospectively from 2001 to 2014 using standard clinical protocols in the context of daily practice<sup>15</sup> at the Rheumatology Unit of University Federico II of Naples.

All patients were classified on the basis of CASPAR criteria, applied either at the time of diagnosis (if observed after 2006) or retrospectively (if observed before 2006 and then obtaining first diagnosis using Moll and Wright criteria)<sup>7,8</sup>.

Our observational study was conducted in a routine clinical setting, where DMARD and anti-TNF agents were prescribed on the basis of current recommendations, as part of the usual standard of care<sup>15</sup>. The exclusion criterion was a personal history of malignancy.

At first visit, as well as at each 3-4 month followup visit, according to standardized clinical practice, medical history and physical and laboratory findings were recorded. Information on the presence of comorbidities, as well as malignancies, was collected. At each visit, eventual data were recorded on laboratory, radiography, and pathology tests, confirming malignancy diagnosis, when present. In addition, date of diagnosis, and type and site of malignancy (coded according to the International Classification of Diseases, Ninth Revision) were recorded. Other data assessed at each visit were smoking habits and family history of malignancies.

With an expected difference in the risk of cancer of at least 40% between the 2 treatments groups, the sample size was calculated in a minimum of 200 patients for each arm.

The study was approved by the Local Ethics Committee "C. Romano," with number 910.

**Statistical analysis.** Statistical analysis was performed with the SPSS 17 system (SPSS Inc.). Continuous data were expressed as mean  $\pm$  SD; categorical variables were expressed as percentages. The Student t test was performed to compare continuous variables; the chi-square test was done to analyze categorical data. When the minimum expected value was  $< 5$ , the Fisher's exact test was used.

A Kaplan-Meier survival model (with the log-rank test) was adopted to evaluate the cumulative incidence of malignancy according to the type of antirheumatic treatment (traditional therapy vs biologic therapy). To adjust for all the other clinical and demographic variables and to evaluate the incidence of malignancy, a Cox regression analysis (stepwise method) was adopted. Occurrence of malignancy was used as the dependent variable. All potential confounding factors were included as follows: age, sex, smoking habits, duration of observation, family history of malignancy, and type of antirheumatic treatment, as independent variables. Multicollinearity effect in multivariable regression models was excluded by a stepwise approach with each variable included for  $p < 0.05$  and excluded for  $p > 0.1$ . All the results are presented as 2-tailed values with statistical significance if  $p$  values were  $< 0.05$ .

## RESULTS

A total of 618 patients with PsA (241 men and 377 women; mean age  $\pm$  SD: 52.1  $\pm$  12.8 yrs) with a median followup of 9 years (range: 2-14 yrs; 5562 patient-yr) were included in the study. Demographic and clinical characteristics of 2 groups of patients are reported in Table 1.

At baseline, in patients taking anti-TNF and DMARD, the most prevalent comorbidities were, respectively, hypertension (55% vs 49.57%), metabolic syndrome (41% vs 39.07%), obesity (38% vs 41.36%), and diabetes (11% vs 16.74%); and thyroid (12% vs 13.84%), upper gastrointestinal (9% vs 12.51%), and nephropathy (1.4% vs 2.3%) disorders.

Of the 322 patients treated with DMARD, 159 (49.3%) were taking MTX, 80 (24.8%) SSZ, 25 (7.7%) CSA, 21

**Table 1.** Demographic and clinical characteristics of patients with PsA included in the study. Data expressed as mean  $\pm$  SD, unless otherwise indicated.

Variables	DMARD	Anti-TNF Agents
Number	322	296
Female, n (%)	199 (62)	178 (60)
Age, yrs	57.2 $\pm$ 12.4	47.5 $\pm$ 22.5
Smokers, n	109	103
Familial history of malignancies, n (%)	47 (15)	151 (51)
Incidence of malignancies (%)	9.3	4.7
TJC	19.5 $\pm$ 4.5	16.8 $\pm$ 7.1
SJC	3.2 $\pm$ 2.2	2.1 $\pm$ 1.9
PASI	6.7 $\pm$ 3.9	4.9 $\pm$ 2.6
HAQ	2.1 $\pm$ 1.1	1.9 $\pm$ 0.5
Patient pain score	64.3 $\pm$ 18.3	61.1 $\pm$ 13.5
Tender enthesal count	7.2 $\pm$ 3.1	6.5 $\pm$ 2.2

PsA: psoriatic arthritis; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; TJC: tender joint count; SJC: swollen joint count; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire.

(6.5%) LEF, and 4 (1.2%) azathioprine (AZA). Fifteen (4.6%) used a combined therapy of MTX plus SSZ, 9 (2.7%) MTX plus AZA, 5 (1.5%) MTX plus CSA, and 4 (1.2%) MTX plus LEF (Table 2).

Among 296 patients treated with anti-TNF agents, 126 (42.5%) were treated with ETN, 116 (39.1%) ADA, 35 (11.8%) IFX, and 19 (6.4%) GOL.

During the observation period, in the total group, 44 patients (7.1%) had a diagnosis of malignancy with a median time from start of therapy to malignancy diagnosis of 3 years (range: 1-8 yrs). When the population was stratified according to the type of therapy administered, patients developing malignancy were distributed as follows: 14 (4.7%; 95% CI 2.8–7.8; 0.52 cases/100 patient-yrs) of 296 subjects receiving anti-TNF therapy, and 30 (9.3%; 95% CI 6.6–13.0;

1.03 cases/100 patient-yrs) of 322 receiving traditional DMARD ( $p = 0.019$  in univariate analysis). In detail, among anti-TNF patients, time to malignancy diagnosis was 3.6 years (median; range 1–7 yrs), and among DMARD users, 3 years (median; range 1–8 yrs).

Among 14 patients treated with anti-TNF agents and having a diagnosis of malignancy, 8 were receiving combination therapy with MTX, and 6 monotherapy (Figure 1).

The different incidence of crude data between patients taking anti-TNF agents and DMARD therapy was confirmed by the Kaplan-Meier survival curve (log-rank test 4.45,  $p = 0.035$ ). However, after adjusting for major clinical and demographic characteristics (age, sex, smoking habits, duration of observation, family history of malignancy, and therapy), the difference between the 2 treatments was no longer significant ( $p = 0.480$ ) and the only predictor of malignancy occurrence was the age (HR 1.04, 95% CI 1.009–1.073,  $p = 0.012$ ).

In Tables 2 and 3, we report the frequency, site, and type of malignancy for each therapy. Some of the more frequently observed malignancies are skin cancer, breast cancer, and meningioma.

## DISCUSSION

Our study focuses on a cohort of 618 patients with PsA observed in an outpatient clinic. Among them, 296 were taking anti-TNF agents and 322 DMARD. The results show a total of 44 patients (7.1%) with a diagnosis of malignancies during a mean followup period of 9 years, for a total of 5562 patient-years. In detail, 14 cases (4.7%) were reported among patients taking anti-TNF therapy and 30 (9.3%) among those taking traditional DMARD. When adjusting for major clinical and demographic characteristics, the difference between the 2 treatments was no longer significant and the only predictor of malignancy occurrence was age.

**Table 2.** Frequency, site, and type of malignancies in our PsA cohort taking traditional DMARD therapy.

No. Patients Taking Various DMARD	No. Patients Showing Malignancies (%)	Site and Type of Malignancies (no. patients)
159; MTX	15 (4.6)	Squamous cell skin carcinoma (2); breast cancer (2); meningioma (2); colon-rectum carcinoma (1); kidney carcinoma (1); ovarian cancer (1); prostate cancer (1); non-Hodgkin lymphoma (1); uterine cancer (1); squamous cell carcinoma of the tongue (1); seminoma (1); papillary thyroid carcinoma (1)
80; SSZ	5 (1.5)	Bladder cancer (2); breast carcinoma (2); uterine cancer (1)
25; CSA	1 (0.3)	Squamous cell skin carcinoma (1)
21; LEF	3 (0.9)	Carcinoid (2); meningioma (1)
4; AZA	1 (0.3)	Breast cancer (1)
15; MTX plus SSZ	3 (0.9)	Melanoma (2); colon-rectum carcinoma (1)
9; MTX plus AZA	2 (0.6)	Melanoma (2)
5; MTX plus CSA	1 (0.3)	Seminoma (1)
4; MTX plus LEF	1 (0.3)	Breast cancer (1)

PsA: psoriatic arthritis; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; SSZ: sulfasalazine; CSA: cyclosporine; LEF: leflunomide; AZA: azathioprine.

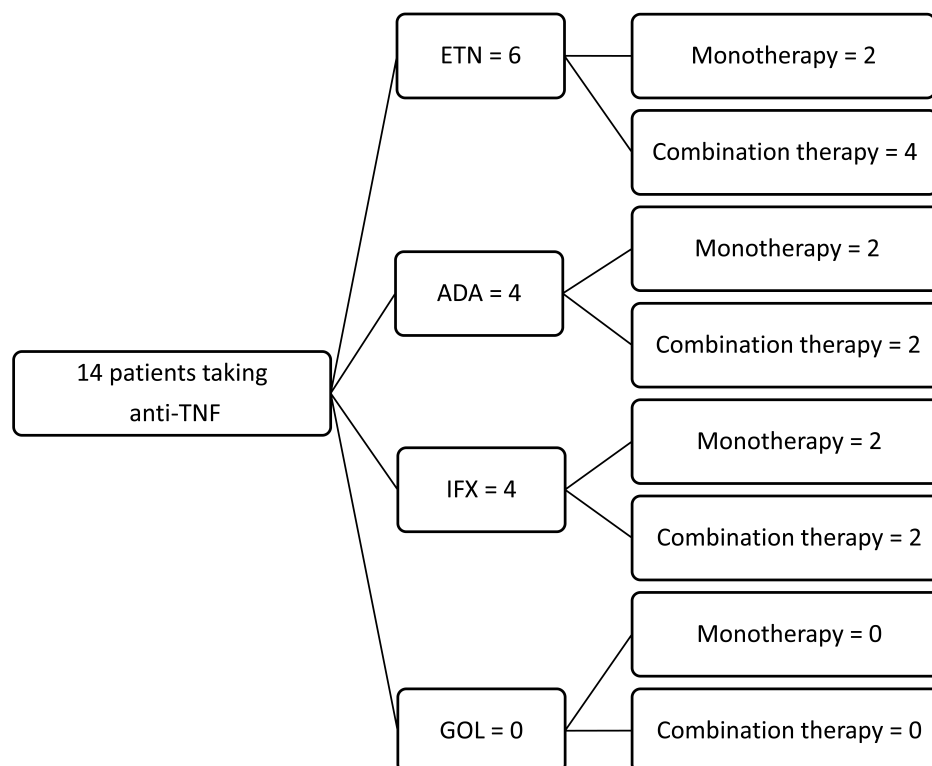


Figure 1. Types of therapies received by the patients treated with anti-TNF agents and having a diagnosis of malignancy. TNF: tumor necrosis factor; ETN: etanercept; ADA: adalimumab; IFX: infliximab; GOL: golimumab.

Table 3. Frequency, site, and type of malignancies in our PsA cohort taking biological therapy.

No. Patients Taking Various Anti-TNF Agents	No. Patients Showing Malignancies (%)	Site and Type of Malignancies (no. patients)
126; ETN	6 (2)	Lung carcinoma (2); ovarian teratoma (1); breast cancer (1); bladder carcinoma (1); squamous cell skin carcinoma (1)
116; ADA	4 (1.3)	Basal cell carcinomas (2); squamous cell carcinoma of the tongue (1); breast cancer (1)
35; IFX	4 (1.3)	Renal carcinoma (1); papillar carcinoma of the thyroid (1); meningioma (1); Kaposi sarcoma (1)
19; GOL	—	—

PsA: psoriatic arthritis; TNF: tumor necrosis factor; ADA: adalimumab; ETN: etanercept; GOL: golimumab; IFX: infliximab.

A study limitation was that patients taking anti-TNF agents are often screened for previous malignancies. This may have caused some selection bias for the development of malignancies in this group.

In line with our study results, an observational study from the British Society for Rheumatology Biologics Register showed that anti-TNF therapy in 600 patients with PsA had a safety profile similar to a control group of 1115 seronegative patients with RA who were taking DMARD. In addition, incidence rate ratios for serious adverse events in

patients with PsA were not increased (0.9; 95% CI 0.8–1.3), when compared to patients with RA taking DMARD<sup>32</sup>.

Recently, Gross, *et al* performed a large study to compare the incidence rates of malignancies among 2970 patients with PsA (7133 patient-yr of followup) and 19,260 patients with rheumatoid arthritis (53,864 patient-yr of followup) included in the CORRONA (Consortium of Rheumatology Researchers of North America) registry<sup>33</sup>. The results showed 40 and 307 malignancies, respectively, in patients with PsA and RA, with an overall malignancy incidence per 100



patient-years similar between patients with PsA and patients with RA [0.56, 95% CI 0.40–0.76; and 0.56, 95% CI 0.50–0.63, respectively]<sup>33</sup>.

The BIOBADASER registry (a Spanish registry for adverse events from biological therapies in rheumatic disease) reported that the standardized incidence ratio (SIR) of cancer in 730 patients with PsA taking anti-TNF agents (exposure: 2323 patient-yrs) did not differ significantly from the general population. The malignancies with higher SIR among patients with PsA enrolled in this registry were 4.84 (0.59–17.48) for non-Hodgkin lymphoma and 3.13 (0.08–17.43) for kidney cancer<sup>34</sup>.

In addition, the results of our study showed that the most frequently observed malignancies, regardless of the therapy, are skin cancer, breast cancer, and meningioma. Some studies have shown that patients with psoriatic diseases and those with PsA had an increased risk for malignancies, in particular lung, lymphoproliferative, and skin malignancies<sup>21,22,23,24,25,26,27,28</sup>. The risk of oncologic diseases, especially the occurrence of skin cancer, described in patients with psoriatic diseases who are taking DMARD (MTX and CSA), has been in part considered related to PUVA exposure<sup>26,28,29</sup>.

Over the last decade, novel therapies have raised expectations, and rheumatologists have proceeded with the high degree of professionalism needed to offer the best care and to reduce the risk of any adverse event. In daily clinical practice, the appropriate identification of patients eligible for these treatments has depended on taking all aspects of a patient's history into account, such as previous or ongoing comorbidities and related therapies, malignancies, and chronic infections or recurrence of acute infections<sup>9,25,26,27,28,29,35–45</sup>.

In the last few years, in addition to enhanced effectiveness due to close monitoring by experienced clinicians, remarkable changes have been obtained in the field of safety. Our study supports that biological therapies, when adequately performed and with proper followup, do not lead to any increased risk for cancer development. Today, in clinical practice, a correct use of both DMARD and anti-TNF agents is essential in the management of PsA and in related therapies.

## REFERENCES

- Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55–78.
- Soscia E, Sirignano C, Catalano O, Atteno M, Costa L, Caso F, et al. New developments in magnetic resonance imaging of the nail unit. *J Rheumatol Suppl* 2012;89:49–53.
- Costa L, Caso F, D'Elia L, Atteno M, Peluso R, Del Puente A, et al. Psoriatic arthritis is associated with increased arterial stiffness in the absence of known cardiovascular risk factors: a case control study. *Clin Rheumatol* 2012;31:711–5.
- Shang Q, Tam LS, Sanderson JE, Sun JP, Li EK, Yu CM. Increase in ventricular-arterial stiffness in patients with psoriatic arthritis. *Rheumatology* 2015;51:2215–23.
- Haroon M, Gallagher P, Heffernan E, FitzGerald O. High prevalence of metabolic syndrome and of insulin resistance in psoriatic arthritis is associated with the severity of underlying disease. *J Rheumatol* 2014;41:1357–65.
- Scarpa R, Ayala F, Caporaso N, Olivieri I. Psoriasis, psoriatic arthritis, or psoriatic disease? *J Rheumatol* 2006;33:210–2.
- Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
- Tillett W, Costa L, Jadon D, Wallis D, Cavill C, McHugh J, et al. The CLASSification for Psoriatic ARthritis (CASPAR) criteria—a retrospective feasibility, sensitivity, and specificity study. *J Rheumatol* 2012;39:154–6.
- Joshi P, Dhaneshwar SS. An update on disease modifying antirheumatic drugs. *Inflamm Allergy Drug Targets* 2014;13:249–61.
- Suryaprasad AG, Prindiville T. The biology of TNF blockade. *Autoimmun Rev* 2003;2:346–57.
- Raychaudhuri SP. Role of IL-17 in psoriasis and psoriatic arthritis. *Clin Rev Allergy Immunol* 2013;44:183–93.
- Fiocco U, Accordi B, Martini V, Oliviero F, Faccio M, Cabrelle A, et al. JAK/STAT/PKC $\delta$  molecular pathways in synovial fluid T lymphocytes reflect the in vivo T helper-17 expansion in psoriatic arthritis. *Immunol Res* 2014;58:61–9.
- Fiocco U, Sfriso P, Oliviero F, Lunardi F, Calabrese F, Scagliori E, et al. Blockade of intra-articular TNF in peripheral spondyloarthritis: its relevance to clinical scores, quantitative imaging and synovial fluid and synovial tissue biomarkers. *Joint Bone Spine* 2013;80:165–70.
- Fiocco U, Martini V, Accordi B, Caso F, Costa L, Oliviero F, et al. Transcriptional network profile on synovial fluid T cells in psoriatic arthritis. *Clin Rheumatol* 2015;34:1571–80.
- Salvarani C, Pipitone N, Marchesoni A, Cantini F, Cauli A, Lubrano E, et al; Italian Society for Rheumatology. Recommendations for the use of biologic therapy in the treatment of psoriatic arthritis: update from the Italian Society for Rheumatology. *Clin Exp Rheumatol* 2011;29:S28–41.
- Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, FitzGerald O, Winthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2012;71:319–26.
- Armstrong AW, Coates LC, Espinoza LR, Ogdie AR, Rich P, Soriano ER. Infectious, oncologic, and autoimmune comorbidities of psoriasis and psoriatic arthritis: a report from the GRAPPA 2012 annual meeting. *J Rheumatol* 2013;40:1438–41.
- Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982–1991. *J Rheumatol* 2000;27:1247–50.
- Rohekar S, Tom BD, Hassa A, Schentag CT, Farewell VT, Gladman DD. Prevalence of malignancy in psoriatic arthritis. *Arthritis Rheum* 2008;58:82–7.
- Haynes K, Beukelman T, Curtis JR, Newcomb C, Herrinton LJ, Graham DJ, et al; SABER Collaboration. Tumor necrosis factor  $\alpha$  inhibitor therapy and cancer risk in chronic immune-mediated diseases. *Arthritis Rheum* 2013;65:48–58.
- Frentz G, Olsen JH. Malignant tumours and psoriasis: a follow-up study. *Br J Dermatol* 1999;140:237–42.
- Boffetta P, Gridley G, Lindelöf B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. *J Invest Dermatol* 2001;117:1531–7.
- Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. *Arch Dermatol* 2001;137:778–83.
- Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. *Arch Dermatol* 2003;139:1425–9.

25. Stern RS. Lymphoma risk in psoriasis: results of the PUVA follow-up study. *Arch Dermatol* 2006;142:1132-5.
26. Archier E, Devaux S, Castela E, Gallini A, Aubin F, Le Maître M, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2012;26 Suppl 3:22-31.
27. Stern RS, Bagheri S, Nichols K. The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. *J Am Acad Dermatol* 2002;47:33-9.
28. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet* 2001;358:1042-5.
29. van Lümig PP, Menting SP, van den Reek JM, Spuls PI, van Riel PL, van de Kerkhof PC, et al. An increased risk of non-melanoma skin cancer during TNF-inhibitor treatment in psoriasis patients compared to rheumatoid arthritis patients probably relates to disease-related factors. *J Eur Acad Dermatol Venereol* 2015;29:752-60.
30. Nannini C, Cantini F, Niccoli L, Cassarà E, Salvarani C, Olivieri I, et al. Single-center series and systematic review of randomized controlled trials of malignancies in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis receiving anti-tumor necrosis factor alpha therapy: is there a need for more comprehensive screening procedures? *Arthritis Rheum* 2009;61:801-12.
31. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol* 2011;64:1035-50.
32. Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL; BSRBR. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. *Rheumatology* 2010;49:697-705.
33. Gross RL, Schwartzman-Morris JS, Krathen M, Reed G, Chang H, Saunders KC, et al. A comparison of the malignancy incidence among patients with psoriatic arthritis and patients with rheumatoid arthritis in a large US cohort. *Arthritis Rheumatol* 2014;66:1472-81.
34. Carmona L, Abasolo L, Descalzo MA, Pérez-Zafra B, Sellas A, de Abajo F, et al; BIOBADASER Study Group; EMECAR Study Group. Cancer in patients with rheumatic diseases exposed to TNF antagonists. *Semin Arthritis Rheum* 2011;41:71-80.
35. Costa L, Caso F, Atteno M, Del Puente A, Darda MA, Caso P, et al. Impact of 24-month treatment with etanercept, adalimumab, or methotrexate on metabolic syndrome components in a cohort of 210 psoriatic arthritis patients. *Clin Rheumatol* 2014;33:833-9.
36. Jókai H, Szakonyi J, Kontár O, Marschalkó M, Szalai K, Kárpáti S, et al. Impact of effective tumor necrosis factor- $\alpha$  inhibitor treatment on arterial intima-media thickness in psoriasis: results of a pilot study. *J Am Acad Dermatol* 2013;69:523-9.
37. Di Minno MN, Iervolino S, Peluso R, Scarpa R, Di Minno G; CaRRDs study group. Carotid intima-media thickness in psoriatic arthritis: differences between tumor necrosis factor- $\alpha$  blockers and traditional disease-modifying antirheumatic drugs. *Arterioscler Thromb Vasc Biol* 2011;31:705-12.
38. Avgerinou G, Tousoulis D, Siasos G, Oikonomou E, Maniatis K, Papageorgiou N, et al. Anti-tumor necrosis factor  $\alpha$  treatment with adalimumab improves significantly endothelial function and decreases inflammatory process in patients with chronic psoriasis. *Int J Cardiol* 2011;151:382-3.
39. Atteno M, Costa L, Matarese A, Caso F, Del Puente A, Cantarini L, et al. The use of TNF- $\alpha$  blockers in psoriatic arthritis patients with latent tuberculosis infection. *Clin Rheumatol* 2014;33:543-7.
40. Costa L, Caso F, Atteno M, Giannitti C, Spadaro A, Ramonda R, et al. Long-term safety of anti-TNF- $\alpha$  in PsA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. *Clin Rheumatol* 2014;33:273-6.
41. Fabbri M, Cantarini L, Caso F, Costa L, Pagano VA, Frediani B, et al. Drug retention rates and treatment discontinuation among anti-TNF- $\alpha$  agents in psoriatic arthritis and ankylosing spondylitis in clinical practice. *Mediators Inflamm* 2014;2014:862969.
42. Pompili M, Biolato M, Miele L, Grieco A. Tumor necrosis factor- $\alpha$  inhibitors and chronic hepatitis C: a comprehensive literature review. *World J Gastroenterol* 2013;19:7867-73.
43. Temel T, Cansu DÜ, Korkmaz C, Kaşifoğlu T, Özakıoğlu A. The long-term effects of anti-TNF- $\alpha$  agents on patients with chronic viral hepatitis C and B infections. *Int J Rheum Dis* 2015;18:40-5.
44. Caso F, Cantarini L, Morisco F, Del Puente A, Ramonda R, Fiocco U, et al. Current evidence in the field of the management with TNF- $\alpha$  inhibitors in psoriatic arthritis and concomitant hepatitis C virus infection. *Expert Opin Biol Ther* 2015;15:641-50.
45. Di Minno MN, Iervolino S, Lupoli R, Russolillo A, Coppola A, Peluso R, et al. Cardiovascular risk in rheumatic patients: the link between inflammation and atherothrombosis. *Semin Thromb Hemost* 2012;38:497-505.