

Data on the Safety of Psoriasis Therapies

Craig L. Leonardi, MD*

■ Abstract

Safety remains paramount to the clinical utility of a therapy. Evaluation of safety is an ongoing process that does not end when a therapy becomes commercially available. This article reviews recent data pertaining to the safety profile of two therapeutic classes widely used in the treatment of psoriasis: inhibitors of tumor necrosis factor- α and agents that target interleukin-12/23.

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■ Keywords

Tumor necrosis factor; interleukin-12; interleukin-23; rheumatoid arthritis; psoriasis; Janus kinase inhibitor

Ensuring the safety of a therapy involves accumulation and analysis of data from all phases of an agent's clinical history, including registration trials (phase I, II, and III), registry data, Food and Drug Administration Adverse Event Reporting System (AERS), and postmarketing surveillance.

Registration trials have several limitations that complicate assessment of a drug's safety. The trials involve relatively few patients, and the duration of exposure to placebo control tends to be brief, usually 12 and 16 weeks, as is the follow-up period.

Concepts about long-term follow-up have evolved as experience with biologic therapies has increased. Initially, 24 weeks was considered a long-term extension trial. Today, extension studies often continue for 4 years after completion of a 1-year clinical trial.

One notable example illustrates the need to gather safety information from multiple sources and to make monitoring of safety a continuous process. The T-cell inhibitor efalizumab

was withdrawn from the US market because of a higher-than-expected incidence of progressive multifocal leukoencephalopathy (PML) that became apparent only after long-term use of the drug.¹ (The drug remains available in some other countries, and no other cases of PML have been reported since withdrawal of efalizumab in the United States.)

TNF Inhibitors

A well-respected group of clinical researchers evaluated the risk of infection and malignancy in five tumor necrosis factor (TNF)- α inhibitors in a meta-analysis of 20 published clinical trials involving 6,810 patients with psoriatic disease.² The analysis showed a slightly higher risk of infection in patients treated with TNF inhibitors but no increase in the risk of serious infections or malignancies. The principal limitation of the data was short-term follow-up for detection of cancer and determining infection rates.

The same group of researchers examined the risk of myocardial infarction (MI) in British patients with psoriasis.³ The analysis showed that patients with severe psoriasis had a significantly increased risk of MI in comparison with patients who had mild disease. Younger patients with severe disease had the highest risk of MI. The study played a major role in raising awareness among dermatologists of the association between psoriasis and cardiovascular disease.

Rheumatologists have accumulated far more clinical experience with TNF inhibitors in rheumatoid arthritis (RA) than have clinicians who manage psoriasis. Many nations other than the United States have large registry databases related to use of TNF inhibitors, and researchers have provided valuable insights regarding the association between TNF inhibitors and disease outcomes. For example, a Scandinavian study showed that patients with RA had a 35% lower mortality risk when treated with TNF inhibitors than did control groups.⁴

Another study from Scandinavia examined the association between treatment with TNF inhibitors and cardiovascular clinical events in patients with RA.⁵ The results showed a 54% reduction in the risk of cardiovascular events in patients treated with TNF inhibitors versus patients who received control therapies. More recently, a meta-analysis showed a 48% reduction in the risk of MI in patients with psoriasis treated with TNF inhibitors.⁶

Anti-IL-12/23 Therapy

Analysis of safety in agents that target interleukin (IL)-12/23 has yielded somewhat different results from those associated with TNF inhibitors. An overall safety analysis produced no evidence related to the risk of major adverse cardiac events (MACE) in placebo-controlled trials of ustekinumab. However, an analysis that separated the control period from follow-up suggested an increased risk of MACE during early use of ustekinumab.⁷

*Clinical Professor of Dermatology, Saint Louis University Central Dermatology, St Louis, MO.

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Address reprint requests to: Craig L. Leonardi, MD, Central Dermatology, 1034 S. Brentwood Boulevard, St Louis, MO 63117; craig.leonardi@centralderm.com.

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In a subsequent meta-analysis, MACE rates were compared from psoriasis trials involving various types of biologic agents (Table).⁸ The results showed 10 cases of MACE in patients treated with IL-12/23 inhibitors versus one in patients treated with TNF inhibitors, and none in patients randomized to placebo. The difference did not achieve statistical significance ($P=0.11$), but the results suggested a possible safety issue.

Another meta-analysis employed a statistical technique that takes into account rare events.⁹ The results did show a significantly higher risk of MACE in groups treated with IL-12/23 inhibitors than in control groups.

Trials of psoriasis therapies have lacked statistical power to evaluate MACE and instead are powered to determine the efficacy of a therapy. Nonetheless, the consistency of the signal raises questions about this class of agent.

Biologic Therapy and Cancer Risk

A drug's malignancy potential always attracts interest and scrutiny. The rheumatology community has accumulated substantially more data on this issue than have their counterparts

in dermatology. Because many agents are used in both RA and psoriatic disease, the rheumatology data have relevance to the dermatology community.

One of the most comprehensive studies of biologic therapy and cancer risk involved a national database comprising 13,869 patients with RA, 6,597 of whom were treated with biologic agents.¹⁰ The patients had a total follow-up of 49,000 patient-years, and all patients had been treated for at least 1 year.

An analysis of the database showed no significantly increased risk of any nonskin cancer malignancies. Treatment with biologic therapies was associated with an odds ratio of 1.5 for nonmelanoma skin cancer compared with other types of therapies.¹⁰

In some cases, a statistically significant increase in cancer risk is not necessary to attract attention. A case in point is tofacitinib, another targeted agent used to treat RA. Follow-up from initiation of treatment to 24 months showed a small but consistent increase in the malignancy rate among patients treated with tofacitinib.¹¹

■ **TABLE** Summary of MACE in Randomized Controlled Psoriasis Trials (Meta-Analysis)

	Study author	Biologic agent	Mean baseline PASI	Mean baseline BSA (%)	No. of patients who received ≥ 1 dose		MACE during PCP		Duration of PCP (weeks)
					Biologic	Placebo	Biologic	Placebo	
1	Krueger	Ustekinumab	19.1	27.2	254	64	3	0	20
2	Leonardi	Ustekinumab	20.2	26.7	510	255	1	0	12
3	Papp	Ustekinumab	19.6	26.4	820	410	1	0	12
4	Kimball	ABT-874	19	26	150	30	0	0	12
5	M06-890	ABT-874	19.2	25.1	981	484	5	0	12
6	M10-114	ABT-874 Etanercept	18.8	23.8	138 141	68	0 0	0 0	12
7	M10-315	ABT-874 Etanercept	18.8	24.2	139 139	72	0 0	0 0	12
8	Chaudhari	Infliximab	23	NA	22	11	0	0	10
9	Gottlieb	Infliximab	19	27	197	51	0	0	10
10	Reich	Infliximab	22.9	34	301	77	0	0	24
11	Menter	Infliximab	20.1	28.4	627	208	0	0	14
12	Leonardi	Etanercept	18.7	28.7	486	166	0	0	12
13	Gottlieb	Etanercept	18.6	32	57	55	0	1	24
14	Papp	Etanercept	16.4	23	390	193	0	0	12
15	Tyring	Etanercept	18.2	27.2	311	307	0	0	12
16	Van de Kerkhof	Etanercept	21.2	28.4	96	46	0	0	12
17	Gordon	Adalimumab	15.7	27.3	95	52	1	0	12
18	Menter	Adalimumab	18.9	25.7	814	398	0	0	16
19	Asahina	Adalimumab	28.4	46.2	123	46	0	0	24

MACE=major adverse cardiac events; PASI=Psoriasis Area Severity Index; PCP=placebo-controlled phase.

Source: Adapted from Ryan et al.⁸ Used with permission.

Follow-up of tofacitinib-treated patients beyond 42 months did not show any obvious increase in the malignancy rate, but the rate did not decline. The absence of a clear decline is noteworthy because adverse events tend to decrease over time, as clinicians learn which patients respond to therapy and have few adverse events.

The PSOLAR Experience

An ongoing multicenter observational study will provide data on the long-term safety and clinical outcomes with therapies given to patients with moderate to severe psoriasis. The Psoriasis Longitudinal Assessment and Registry (PSOLAR) has a target enrollment of 12,000 patients, who will be followed for 8 years or longer. Investigators at 266 sites in 15 countries are enrolling patients.¹²

Patients enrolled in PSOLAR receive treatment that is based on usual clinical practice and standard of care. A key objective is to accumulate data that reflect “real-world” experience in the treatment of psoriasis.

Preliminary unadjusted data based on few clinical events have shown no major differences in malignancy rates among patients treated with an IL-12/23 inhibitor, TNF inhibitors, other biologics, or nonbiologic therapy.¹³

Analysis of serious infections showed the highest rate among patients treated with infliximab and the lowest in patients who received the IL-12/23 inhibitor ustekinumab.¹⁴ MACE rates were fairly evenly distributed among ustekinumab, TNF inhibitors, and other biologics. Patients who received no biologic therapy (mostly older patients treated with phototherapy) had the highest rate.¹⁵

PSOLAR is the largest registry of its kind and will provide the data needed to address longitudinal questions such as the natural course of the disease, development of comorbid diseases, and treatment-specific issues (infection, cancer, MACE, and unanticipated events).

Summary

The safety of a therapy cannot be determined on the basis of a single source of data. Safety assessment is an ongoing process that involves input from multiple sources. The long-term safety of psoriasis therapies has lagged behind that of other diseases and specialties, but data from the rheumatology community have been informative. PSOLAR eventually will provide the data necessary to determine the effectiveness and safety of therapies used to treat psoriasis.

References

- Leonardi C, Menter A, Hamilton T, Caro I, Xing B, Gottlieb AB. Efalizumab: Results of a 3-year continuous dosing study for the long-term control of psoriasis. *Br J Dermatol*. 2008;158:1107-1116.
- 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 trials. *J Am Acad Dermatol*. 2011;64:1035-1050.
- Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296:1736-1741.
- Jacobsson LT, Turesson C, Nilsson JA, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:670-675.
- Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol*. 2005;32:1213-1218.
- Wu JJ, Poon KY, Channal JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol*. 2012;148:1244-1250.
- Reich K, Leonardi C, Griffiths CEM, et al. Update on the cumulative safety experience of ustekinumab: Result from the ustekinumab psoriasis clinical development program with up to 4 years of follow-up. Presented at: 22nd World Congress of Dermatology; May 24-29, 2011; Seoul, Korea. Abstract FC07-03.
- Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: A meta-analysis of randomized controlled trials. *JAMA*. 2011;306:864-871.
- Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk of major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: A meta-analysis of randomized controlled trials. *J Eur Acad Dermatol Venereol*. 2013;27:622-627.
- Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. *Arthritis Rheum*. 2007;56:2886-2895.
- Curtis JR, Mariette X, Lee EB, et al. Tofacitinib, an oral Janus kinase inhibitor: An analysis of malignancies across the rheumatoid arthritis clinical program. EULAR 2013. Abstract 802.
- Papp KA, Strober B, Augustin M, et al. PSOLAR: Design, utility, and preliminary clinical results of a prospective, international, disease-based registry of patients with psoriasis who are receiving, or are candidates for, conventional systemic treatments or biologic agents. *J Drugs Dermatol*. 2012;11:1210-1217.
- Langley R, Strober B, Chevrier M, Lebwohl M. Malignancy events in the psoriasis longitudinal assessment and registry (PSOLAR) study: Current status of observations. *J Am Acad Dermatol*. 2013;68(suppl):AB206. P6448.
- Leonardi C, Fiorentino D, Chevrier M, Kalb R. Serious infection events in the psoriasis longitudinal assessment and registry (PSOLAR) study: Current status of observations. *J Am Acad Dermatol*. 2013;68(suppl):AB213. P6343.
- Gottlieb A, Naldi L, Chevrier M, Bissonnette R. Major adverse cardiovascular events in the psoriasis longitudinal assessment and registry (PSOLAR) study: Current status of observations. *J Am Acad Dermatol*. 2013;68(suppl):AB205. P6658.