TRENDS-in-MEDICINE

BULLETIN:

AMERICAN COLLEGE OF RHEUMATOLOGY (ACR): THE SAFETY OF JAK INHIBITORS

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by Lynne Peterson

Two studies presented at the American College of Rheumatology (ACR) meeting both concluded that JAK inhibition with PFIZER's Xeljanz (tofacitinib) is safe in multiple rheumatologic conditions.

SAFETY IN MULTIPLE CONDITIONS

Investigators reported in a late-breaker poster at ACR that they found no evidence of an increased risk of venous thromboembolic events (VTE) in patients in development programs who took tofacitinib for rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, or ulcerative colitis (UC).

Systemic inflammation is a risk factor for VTE, and increased risk of VTE has been reported in patients with RA, psoriasis, and UC compared to the general population as well as in patients with PsA taking disease-modifying anti-rheumatic drugs (DMARDs). A potential increased risk of VTE in patients with RA has been reported for an oral JAK1/2 inhibitor – Pfizer's Xeljanz (tofacitinib) – in treating RA, and it has been evaluated in other inflammatory diseases, including psoriasis, PsA, and UC.

Researchers from institutions including The Swedish Medical Center, the University of Washington, Albany Medical College, and the Mayo Clinic analyzed data from 5,432 patients with RA, including 2,773 patients with psoriasis, 816 patients with PsA, and 1,220 patients with UC. The analysis of deep vein thrombosis (DVT) and pulmonary embolism (PE) events across randomized controlled clinical studies in those patients showed no evidence of an increased risk of events with tofacitinib.

There was no imbalance of DVT or PE events with tofacitinib vs. placebo or active comparators, and no dose-response relationship was reported for tofacitinib 5 mg and 10 mg BID. The incidence rate of DVT events in patients taking tofacitinib was similar to that reported in the literature for patients with RA and PsA.

The researchers concluded, "Overall, these findings do not support a causal relationship between tofacitinib treatment and DVT or PE events. Therefore, it is ***unlikely*** that the JAK inhibitor drug class as a whole is associated with increased risk of VTE.

SAFETY IN RHEUMATOID ARTHRITIS (RA)

An analysis of pooled data from two multicenter, open-label, long-term extension (LTE) studies in rheumatoid arthritis over nine years showed that tofacitinib had a consistent safety profile out to 114 months and sustained efficacy out to 96 months.

The rates of serious adverse events, serious infections, and malignancies were similar to those observed in earlier analyses of long-term extension studies. Patient-level lab safety data were consistent with findings from tofacitinib Phase II and Phase III trials and previous

long-term extension data in patients with RA. Tofacitinib 5 mg and 10 mg BID provided sustained improvement in signs and symptoms of RA, physical function, and patient-reported outcomes out to 96 months in patients who continued treatment. Both the safety and the efficacy of the drug were the same in patients on monotherapy as in combination with DMARDs.

In the study, tofacitinib 5 mg BID and 10 mg BID were given to 4,967 patients, 76.4% of whom continued with their original dose. Over the 114 months, 2,518 patients (50.7%) permanently discontinued. Common reasons for discontinuation included: 16.4% for a drug-related adverse event, 7.5% for an unrelated adverse event, 10.1% were no longer willing to participate, and 3.6% had insufficient clinical responses.

Efficacy was good:

- ACR20, ACR50, and ACR70 response rates for all patients were sustained from Month 1 to Month 96.
- For all patients, mean DAS28-4 decreased in the first month and that was maintained out to Month 96: on average 6.3 at baseline, 3.8 at Month 1 of the extension studies, and 3.3 at Month 96.
- Efficacy results were similar between patients who took tofacitinib as monotherapy and those who took it in combination with a DMARD.
- The ACR20 response rate hovered around 80% from Month 12 through Month 84 and then started to dip slightly for all patients.
- The ACR70 response was ~38% for all patients at Month 12 and gradually increased to ~40% at Week 96, except for patients taking 10 mg BID. Those patients started declining at Week 60.

The most commonly reported classes of treatment-emergent adverse events were infections and infestations (69.6% of patients), musculoskeletal/connective tissue disorders (40.3%), and gastrointestinal disorders (34.1%). The most commonly reported adverse events were nasopharyngitis (19.1%), upper respiratory tract infection (17.9%), bronchitis (12.6%), and urinary tract infections (12.5%). These were consistent with data reported up to Month 105.

Pooled Tofacitinib Safety Data Out to 114 Months					
Measurement	**All tofacitinib (n=4,967)**	**Tofacitinib 5 mg BID (n=1,535)**	**Tofacitinib 10 mg BID (n=3,432)**	**All tofacitinib + DMARD (n=3,215)**	**All tofacitinib monotherapy (n=1,752)**
Total tofacitinib exposure, patient-years (PY)	17,738	5,891	11,847	11,482	6,256
Treatment duration in years	3.5	3.7	3.4	3.5	3.5
Any adverse event	90.9%	92.3%	90.3%	90.7%	91.3%
Discontinuation due to an adverse event	24.9%	27.2%	23.9%	26.3%	22.4%
Most common treatment-emergent adverse events					
Nasopharyngitis	19.1%	24.8%	16.6%	17.7%	21.6%
Upper respiratory tract infection	17.9%	17.7%	18.0%	19.8%	14.4%
Bronchitis	12.6%	12.4%	12.8%	13.7%	10.7%
Urinary tract infection	12.5%	11.0%	13.2%	14.3%	9.4%
Herpes zoster	12.1%	12.7%	11.8%	12.5%	11.3%
Hypertension	10.3%	12.2%	9.5%	10.5%	10.0%
Back pain	9.2%	10.0%	8.8%	9.8%	8.1%

Exposure-adjusted event rates (EAER) are the number of unique events divided by the total exposure in the treatment group in the pooled cohort, per 100 patient-years.

Incidence Rates of Serious Adverse Events of Particular Concern and Other Adverse Events of Special Interest					
Measurement	**All tofacitinib (n=4,967)**	**Tofacitinib 5 mg BID (n=1,535)**	**Tofacitinib 10 mg BID (n=3,432)**	**All tofacitinib + DMARDs (n=3,215)**	**All tofacitinib monotherapy (n=1,752)**
Total tofacitinib exposure, patient-years	17,738	5,891	11,847	11,482	6,256
Incidence rates in patients with events per 100 patient-years (PY)					
Serious adverse events	9.1	8.7	9.4	9.5	8.5
Serious infections	2.5	2.2	2.6	2.5	2.3
Herpes zoster	3.7	3.6	3.8	3.9	3.4
Opportunistic infections (excluding tuberculosis)	0.4	0.2	0.5	0.4	0.4
Tuberculosis	0.1	0.1	0.2	0.1	0.1
Malignancies (excluding NMSC)	0.8	0.9	0.8	0.8	0.9
NMSC	0.7	0.5	0.7	0.7	0.5
MACE	0.4	0.4	0.4	0.4	0.3