

CLINICAL FLASHCARDS

The ORAL Surveillance JAK Inhibitor Controversy

The Life Science Feed

QUESTION

Prior to the biologics revolution, what was the impact of rheumatoid arthritis on life expectancy?



ANSWER

It resulted in a substantially shortened life expectancy.

QUESTION

Which medication is considered the 'anchor drug' for rheumatoid arthritis treatment?

ANSWER

Methotrexate

QUESTION

Name three examples of anti-TNF therapies that arrived in the late 1990s.

ANSWER

Etanercept, infliximab, and adalimumab.

QUESTION

How did the introduction of biologics affect the radiographic progression of rheumatoid arthritis?

ANSWER

It halted radiographic progression.

QUESTION

Besides anti-TNF therapy, name two other specific nodes targeted by biologics in the inflammatory cascade.

ANSWER

IL-6 inhibitors and B cell depletion.

QUESTION

What are the two primary modes of administration for biologic therapies?



ANSWER

Injectable or infusible.

QUESTION

How are JAK inhibitors classified in terms of molecule size?

ANSWER

Small molecules

QUESTION

What is the route of administration for JAK inhibitors?

ANSWER

Oral

QUESTION

What is the primary function of Janus kinase (JAK) enzymes within a cell?

ANSWER

They act as signal transducers relaying signals from cytokine receptors to the nucleus.

QUESTION

How does the targeting mechanism of JAK inhibitors differ from that of biologics?

ANSWER

JAK inhibitors block multiple cytokines simultaneously rather than targeting a single cytokine or receptor.

QUESTION

List four examples of cytokines or signaling proteins blocked by JAK inhibitors.

ANSWER

IL-6, IL-4, IL-13, and interferons.

QUESTION

Which trial compared the efficacy of baricitinib directly to adalimumab in RA patients?

ANSWER

The MONARCH trial.

QUESTION

In the MONARCH trial, how did baricitinib compare to adalimumab regarding DAS28-ESR improvement?

ANSWER

Baricitinib was numerically superior.

QUESTION

What practical clinical advantage do JAK inhibitors offer over biologics regarding administration site reactions?

ANSWER

JAK inhibitors avoid injection site reactions.

QUESTION

What was the specific purpose of the ORAL Surveillance study mandated by the FDA?

ANSWER

To evaluate the safety of tofacitinib compared to anti-TNF therapy in high-cardiovascular-risk patients.

QUESTION

What were the two primary endpoints of the ORAL Surveillance study?

ANSWER

Major adverse cardiovascular events (MACE) and malignancies.

QUESTION

What was the minimum age requirement for participants in the ORAL Surveillance study?

ANSWER

Age 50 or over.

QUESTION

According to ORAL Surveillance, what was the hazard ratio for MACE with tofacitinib compared to anti-TNF?

ANSWER

Approximately 1.33.

QUESTION

According to ORAL Surveillance, what was the hazard ratio for malignancies with tofacitinib compared to anti-TNF?

ANSWER

Approximately 1.48.

QUESTION

Which specific thrombotic event was found to be significantly higher in the tofacitinib arm of ORAL Surveillance?

ANSWER

Pulmonary embolism

QUESTION

What regulatory action did the FDA take following the results of ORAL Surveillance?

ANSWER

It issued a boxed warning for all approved JAK inhibitors.

QUESTION

Under current restrictions, when should JAK inhibitors be used in patients with high cardiovascular risk?

ANSWER

Only after the failure of anti-TNF therapy.

QUESTION

Why is the generalisability of the ORAL Surveillance results to all RA patients often questioned?

ANSWER

The study population was specifically selected for high baseline cardiovascular risk.

QUESTION

How does anti-TNF therapy typically affect cardiovascular risk in patients with systemic inflammation?

ANSWER

Anti-TNF therapy actually reduces cardiovascular risk.

QUESTION

According to 2026 guidelines, which class of therapy is preferred for RA patients with a history of malignancy?

ANSWER

Biologics

QUESTION

At what age do guidelines suggest a preference for biologics over JAK inhibitors if multiple risk factors are present?

ANSWER

Older than 65.

QUESTION

For which patient demographic do JAK inhibitors remain a viable first-line option after methotrexate failure?

ANSWER

Younger patients without cardiovascular or malignancy risk factors.

QUESTION

What is the specific enzyme selectivity of upadacitinib?

ANSWER

It is more selective for JAK1.

QUESTION

Which society's recommendations state that JAK inhibitors and biologics have broadly comparable efficacy?

ANSWER

EULAR (European Alliance of Associations for Rheumatology).

QUESTION

Term: Tofacitinib

ANSWER

Definition: An oral Janus kinase inhibitor studied in the ORAL Surveillance trial.

QUESTION

Term: Small Molecule (in Rheumatology)

ANSWER

Definition: A low molecular weight compound like a JAK inhibitor that can be administered orally.

QUESTION

Term: MACE

ANSWER

Definition: Major adverse cardiovascular events, used as a primary safety endpoint in clinical trials.

QUESTION

How does systemic inflammation in RA contribute to cardiovascular health?

ANSWER

Systemic inflammation is a major driver of cardiovascular disease in RA patients.

QUESTION

In the context of JAK inhibitors, what does 'class effect' refer to regarding regulatory warnings?

ANSWER

The application of safety warnings to all drugs in the category regardless of individual trial data.

QUESTION

Which trial provides some safety reassurance for upadacitinib, although it lacked the head-to-head design of ORAL Surveillance?



ANSWER

SELECT-COMPARE

QUESTION

What is the primary intracellular outcome when JAK enzymes are successfully blocked?

ANSWER

Gene transcription activated by cytokines is inhibited.

QUESTION

Identify the three major rheumatology societies mentioned that updated their guidelines following ORAL Surveillance.

ANSWER

EULAR, ACR, and BSR.

QUESTION

Which specific biologic class is suggested as a preferred alternative to JAKi in high-risk patients besides anti-TNF?

ANSWER

IL-6 inhibitors

QUESTION

What was the non-inferiority status of tofacitinib in the ORAL Surveillance trial?

ANSWER

Tofacitinib failed to meet non-inferiority for MACE and malignancies.

QUESTION

How does the target of co-stimulation blockers differ from that of anti-TNF therapy?

ANSWER

Co-stimulation blockers target a different node in the inflammatory cascade than TNF cytokines.

QUESTION

Why is oral dosing considered a compelling factor for certain RA patients?

ANSWER

It is transformative for patients who refuse injectable or infusible therapy.

QUESTION

According to the transcript, what was the primary limitation of early biologic therapies?

ANSWER

The practical limitation of being large molecules requiring injection or infusion.

QUESTION

What is the intracellular location where JAK inhibitors exert their primary effect?

ANSWER

Intracellularly (within the cell).

QUESTION

The relay of signals from cytokine receptors to the nucleus is known as _____.

ANSWER

Signal transduction

QUESTION

What effect did biologics have on the disability levels of RA patients?



ANSWER

Disability was significantly reduced.

QUESTION

In high-cardiovascular-risk patients, the ORAL Surveillance study compared tofacitinib to _____.

ANSWER

Anti-TNF therapy

QUESTION

How does the selectivity of upadacitinib potentially impact its safety profile compared to earlier JAK inhibitors?

ANSWER

Its JAK1 selectivity is being studied for a potentially more favourable cardiovascular safety profile.

QUESTION

What is the regulatory recommendation for the sequence of therapy in patients over 65 with cardiovascular risk factors?

ANSWER

Biologics are preferred over JAK inhibitors.

QUESTION

Prior to ORAL Surveillance, how did baricitinib perform against adalimumab on the ACR20 endpoint in the MONARCH trial?

ANSWER

Baricitinib was non-inferior to adalimumab.

QUESTION

What must be a key component of the clinical discussion when prescribing a JAK inhibitor to a younger patient in 2026?

ANSWER

An informed discussion regarding the risk-stratified safety profile.