Meet

Kathy C.

Age 46

SANOFI

רח' בני גאון 10,נתניה 4250498, טל 09-8633700 פקס 09-8851444

KEVZARA®
(sarilumab)

CONSIDER KEVZARA® FOR PATIENTS WHOSE RA PROGRESSION IS UNCONTROLLED

Kathy C.

Age 46, uncontrolled on a TNF α inhibitor plus methotrexate

"I've been on a TNFα inhibitor but, over the past 3 months, it's been harder to keep up with my kids."

Hypothetical patient profile.

Models are used for representative purposes only and not actual RA patients.

PHYSICAL FINDINGS/LABORATORY MEASUREMENTS:

- **Swollen joint count: 19**
- **Tender joint count: 28**
- **C-reactive protein (CRP) level: 39 mg/L**
- Some difficulty preparing everyday meals
- Great difficulty reaching far
- Easily fatigued

INDICATION

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate

KEVZARA Israeli SPC as approved / updated in accordance with the instructions of the Ministry of Health
MAT-IL-2000533

When considering a switch from a TNFα inhibitor

SWITCHING TO A DIFFERENT MECHANISM OF ACTION (MOA) MAY HELP TO ACHIEVE IMPROVED PATIENT OUTCOMES[1]

Prospective and observational real-world studies have suggested[1-5]*:

Patients with RA who switch to a biologic with an alternative MOA can achieve greater improvement than switching to another TNFα inhibitor in measures such as[1-5]:

SIGNS AND SYMPTOMS

DISEASE ACTIVITY

PHYSICAL FUNCTION

*Real-world studies did not include sarilumab.

What the most recent ACR and EULAR RA treatment guidelines† have conditionally recommended[7,8]

If treatment target of remission or low disease activity is not achieved in patients with moderate or high disease activity[7,8]:

- Despite the use of methotrexate (MTX) or TNFα inhibitor, treat with a biologic agent with another mode of action or a second TNFα inhibitor

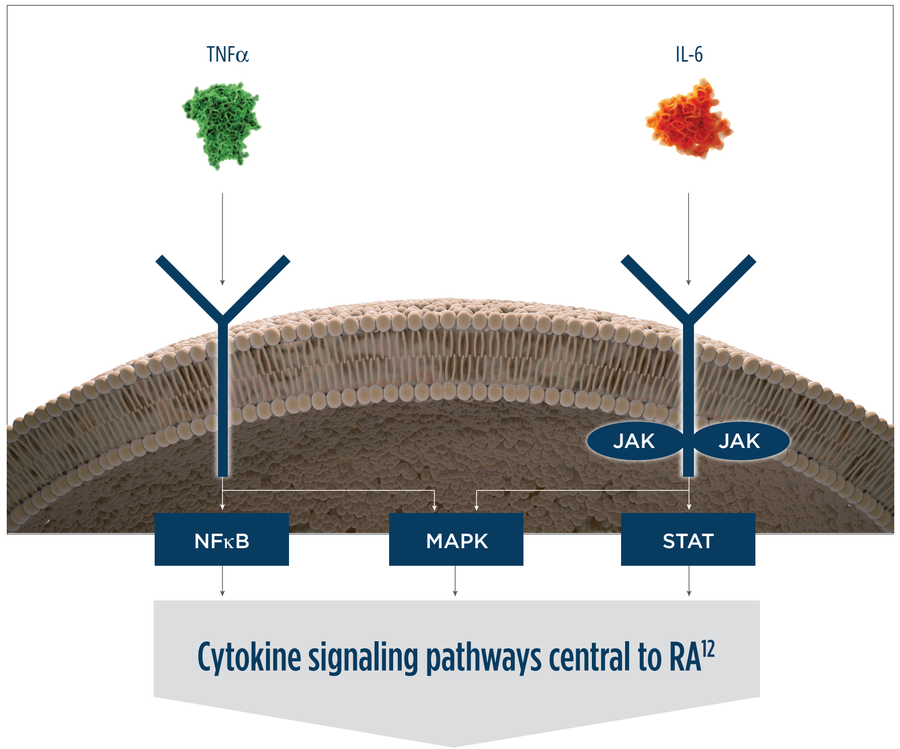
†2019 EULAR Recommendations and 2015 American College of Rheumatology Guidelines.

Patients not reaching their goals may benefit from a new treatment approach[1-5,7,8]

IL-6 PLAYS A CENTRAL ROLE IN RA: PATHOPHYSIOLOGY

- IL-6 is one of the most abundant cytokines in the synovial fluid of the inflamed joints of patients with RA[9]

IL-6 HAS A CENTRAL ROLE IN THE INFLAMMATORY PATHWAYS THAT LEAD TO DISEASE PROGRESSION[10-12]*



Adapted from Choy EH, et al 2013.

- Through its ability to signal soluble and membrane-bound receptors, elevated levels of this multifunctional cytokine have widespread effects[10]
  - Modulating adaptive and innate immune responses

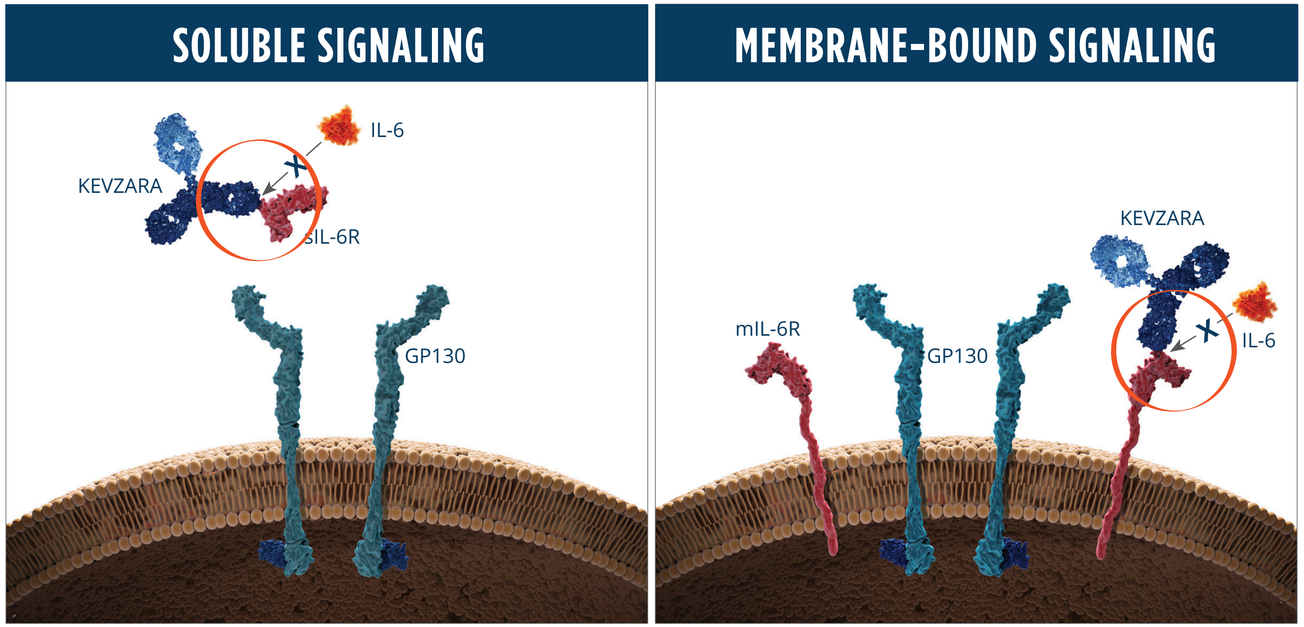
*These mechanisms of action do not necessarily correlate to clinical effects.

When treating RA, take a closer look at the role of IL-6

IL-6=interleukin-6; JAK=janus kinase; MAPK=mitogen-activated protein kinase; NFκB=nuclear factor κB; STAT=signal transducer and activator of transcription; TNF=tumor necrosis factor.

KEVZARA®- TARGETING THE MULTIFUNCTIONAL CYTOKINE IL-6

KEVZARA is a human monoclonal antibody that inhibits IL-6 receptor signaling. KEVZARA targets and binds with high affinity to soluble IL-6 receptors (sIL-6R) and membrane-bound receptors (mIL-6R) [6,13]



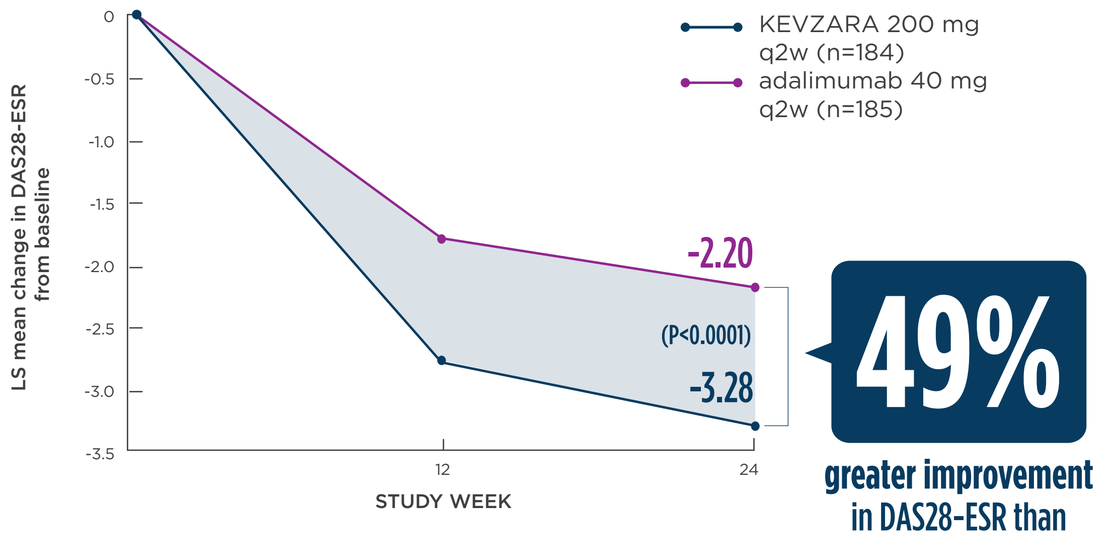
Associated with articular and certain systemic RA symptoms[6,9,13-16]

Elevated levels of IL-6 play a direct role in inflammation and autoimmunity in RA[17,18]

Monotherapy in MTX-IR patients (MONARCH)

KEVZARA®- DEMONSTRATED SUPERIORITY IN DISEASE ACTIVITY (DAS28-ESR) VS ADALIMUMAB

CHANGE IN DAS28-ESR AT WEEK 24*,†



- Nearly 4 times‡ as many patients achieved clinical remission with KEVZARA (27%) than with adalimumab (7%)

*Primary end point; †Reported *P* values are for the difference compared with adalimumab; ‡Relative difference compared with adalimumab was 3.8 times.

MONARCH Study Design[6]: A 24-week, randomized, double-blind, parallel-group study assessing the efficacy and safety of KEVZARA 200 mg q2w monotherapy versus adalimumab 40 mg q2w monotherapy in patients with RA (N=369) who were intolerant of or had an inadequate response to MTX (≥3 months disease duration). Primary objective was to demonstrate KEVZARA superiority to adalimumab, both administered as monotherapy, with respect to signs and symptoms. Change from baseline in DAS28-ESR at week 24 was the primary end point.

LS=least squares.

With KEVZARA, more patients achieved clinical remission compared to adalimumab[6]

KEVZARA®- 200 MG OR 150 MG SUBCUTANEOUS INJECTION: EVERY 2 WEEK DOSING AND ADMINISTRATION

- Recommended starting dose is 200 mg every 2 weeks as a subcutaneous injection
- Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations[6]

AVAILABLE IN 2 DOSAGE STRENGTHS DELIVERED BY PREFILLED PEN*

PREFILLED PEN

*Pen not actual size.

- Should not be stored above 25°C. Do not freeze[6]
- After taking out of refrigerator, do not store back in the refrigerator.
- Prefilled pen should be brought to room temperature 60 minutes prior to use[6]

KEVZARA comes in a prefilled pen that should be stored in the refrigerator, but can be kept at room temperature for up to 14 days[6]

The most frequent adverse reactions observed with Kevzara in clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections. The most common serious adverse reactions were infections.

יש לעיין בעלון לרופא המעודכן כפי שאושר/עודכן בהתאם להוראות משרד הבריאות

KEVZARA®

(sarilumab)

קבזרה כלולה בסל הבריאות וזמינה בכל קופות החולים

References:

1. Gottenberg J-E, Brocq O, Perdinger A, et al. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: A randomized clinical trial. *JAMA.* 2016;316(11):1172-1180.
2. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum.* 2006;54(9):2793-2806.
3. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis.* 2008;67(11):1516-1523.
4. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med.* 2005;353(11):1114-1123.
5. Moots RJ, Naisbett-Groet B. The efficacy of biologic agents in patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor inhibitors: a systematic review. *Rheumatology.* 2012;51(12):2252-2261.
6. KEVZARA Israeli SPC as approved / updated in accordance with the instructions of the Ministry of Health.
7. Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update Ann Rheum Dis 2020;79:685-699
8. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol.* 2016;68(1):1-26.
9. Dayer J-M, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology.* 2010;49:15-24.
10. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford).* 2012;51(suppl 5):v3-v11.
11. Schwartz DM, Bonelli M, Gadina M, O'Shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol.* 2016;12(1):25-36.
12. Choy EH, Kavanaugh AF, Jones SA. The problem of choice: current biologic agents and future prospects in RA. *Nat Rev Rheumatol.* 2013;9(3):154-163.
13. Boyapeti A, Msihid J, Fiore S, et al. Sarilumab plus methotrexate suppresses circulating biomarkers of bone resorption and synovial damage in patients with rheumatoid arthritis and inadequate response to methotrexate: a biomarker study of MOBILITY. *Arthritis Res Ther.* 2016;18(1):225.
14. McInnes IB. Cytokines. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, eds. *Kelley's Textbook of Rheumatology.* Vol 1. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013:369-381.
15. Maggio M, Guralnik J, Longo DL, Ferrucci L. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol A Biol Sci Med Sci.* 2006;61(6):575-584.
16. Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. *Clin Sci (Lond).* 2012;122(4):143-159.
17. Rose-John S, Scheller J, Elson G, Jones SA. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J Leukoc Biol.* 2006;80(2):227-236.
18. Yoshitake F, Itoh S, Narita H, et al. Interleukin-6 directly inhibits osteoclast differentiation by suppressing receptor activator of NF-B signaling pathways. *J Biol Chem.* 2008;283(17):11535-11540.
19. Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a Phase III study. *Arthritis Rheumatol.* 2015;67(6):1424-1437.

SANOFI

רח' בני גאון 10,נתניה 4250498, טל 09-8633700 פקס 09-8851444