14-3-3eta for Rheumatoid Arthritis

Rheumatoid Arthritis Patient Monitoring & Prognosis with 14-3-3eta Testing

augurex

Comprehensive Clinical Overview: 14-3-3eta Efficacy in Monitoring and Prognosis of Rheumatoid Arthritis

In seven studies conducted by five principal investigators from the U.S., Canada, Japan, and Israel, involving over 1,500 patients, serial testing of 14-3-3eta from baseline to multiple subsequent timepoints (2 weeks, 3 months, 5 months, 6 months, 1 year, and up to 60 months) has demonstrated its utility in monitoring rheumatoid arthritis (RA) disease progression and treatment response. Key findings from these studies include:

Baseline Prognosis

14-3-3eta levels ≥0.50 ng/ml at baseline are a strong predictor of poorer clinical and radiographic outcomes, suggesting a worse prognosis.

Modifiability & Treatment Response

14-3-3eta is modifiable and serial decreases in 14-3-3eta and reversion to negative inform better treat-to-target outcomes.

Treatment Agnostic

Improvements in disease activity measures consistently correlate with changes in 14-3-3eta levels throughout the treatment course, across various therapeutic classes such as csDMARDs (methotrexate), TNFi (adalimumab), IL-6Ri (tocilizumab), and JAKi (tofacitinib, upadacitinib).

Persistent Levels Predict Outcomes

When 14-3-3eta levels are ≥0.5 ng/ml, patients are more likely to experience greater joint erosion and have a lower likelihood of achieving or maintaining remission, indicating the need for tighter treatment control.

Enhanced Monitoring with CRP

When used alongside CRP, 14-3-3eta enhances the prediction of disease progression, highlighting its role in refining treatment strategies for high-risk patients.

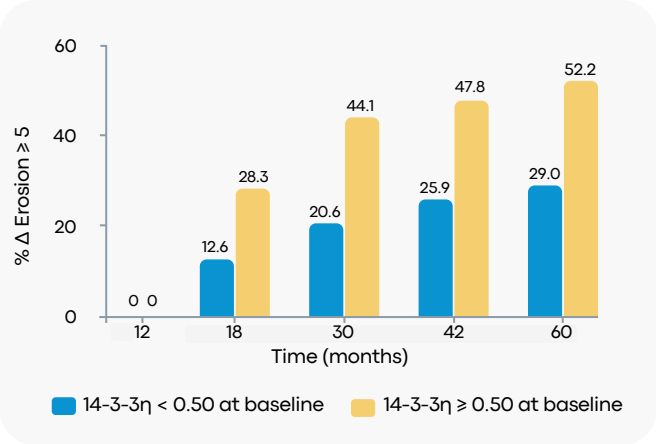
Ongoing Monitoring

14-3-3eta levels are linked to disease activity. Persistent elevation is associated with worse outcomes, while low or negative levels are linked to better outcomes, supporting its use as a valuable biomarker for ongoing disease monitoring and management.

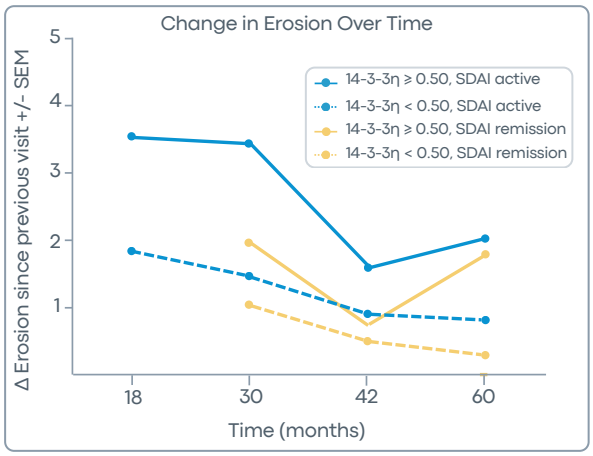
In treat-to-target strategies aimed at achieving clinical and radiographic remission, higher or rising 14-3-3eta levels may signal the need for tighter treatment control. Patients with lower or decreasing 14-3-3eta levels, especially those reverting to negative, are more likely to achieve better clinical and radiographic outcomes, potentially supporting decisions to reduce treatment intensity.

1. Carrier N, Marotta A, de Brum-Fernandes A.J, et al. (2016). Arthritis Research & Therapy, 18:37

Serum Levels of 14-3-3η Protein Supplement C-reactive Protein and Rheumatoid Arthritis-associated Antibodies to Predict Clinical and Radiographic Outcomes in a Prospective Cohort of Patients with Recent-onset Inflammatory Polyarthritis.



- **Patients**: 331 early polyarthritis patients.
- **Timepoints**: Baseline, 12, 18, 30, 42, and 60 months.
- **Treatments**: Methotrexate alone, or in combination with other DMARDs.



Key Findings

- At each time point, 14-3-3eta levels ≥0.50 ng/ml at baseline and after initiation of treatment were associated with lower likelihoods of ever reaching SDAI remission and higher radiographic progression over 5 years.
- Decrease in 14-3-3eta levels during follow ups and reversion to negative were associated with reduced radiographic progression and better long-term outcomes.
- Even if patients are in SDAI remission, sustained levels above ≥0.50 ng/ml led to radiographic progression.

Conclusions: 14-3-3eta ≥0.50 ng/ml at baseline and follow ups predict poorer clinical and radiographic outcomes, even in patients who achieve SDAI remission.

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2. Carrier N, de Brum-Fernandes A.J, Liang P, et al. (2020). RMD Open, 6:1

Impending Radiographic Erosive Progression Over the Following Year in a Cohort of Consecutive Patients with Inflammatory Polyarthritis: Prediction by Serum Biomarkers.

Patients: 749 consecutive patients with early inflammatory polyarthritis.

Timepoints: Baseline, 12, 24, 32, 48, and 60 months.

Treatments: Methotrexate alone, or in combination with other DMARDs.

Key Findings

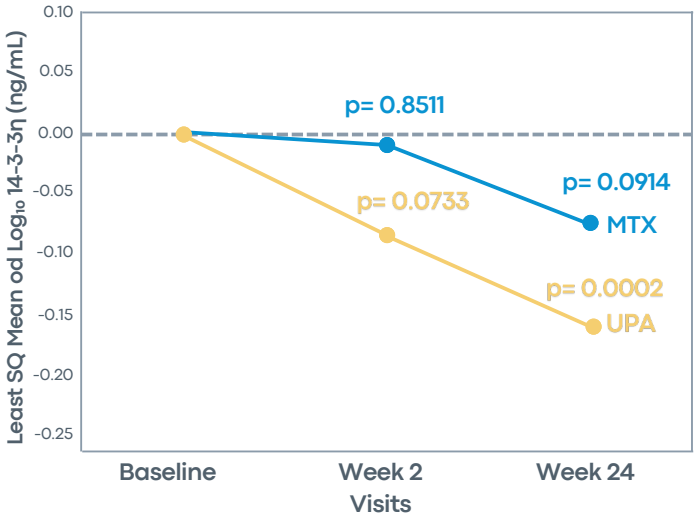
- Elevated 14-3-3eta levels (≥0.50 ng/mL) were associated with an increased risk of rapid erosive progression (REP), especially in patients who also had high CRP levels.
- The predictive value of 14-3-3eta was particularly strong in patients who were non-erosive at baseline, suggesting it could help identify patients at risk for future erosive damage.
- 14-3-3eta levels fluctuated over time, and persistent elevation was linked to worse outcomes, while reversion to negative was associated with lower REP.

Conclusions: 14-3-3eta is a predictor of joint damage progression, especially when used alongside CRP, supporting its use to assess risk, guide treatment, and monitor disease activity.

3. Sornasse T, Chahal S, Gui Y, et al. (2020). Annals of Rheumatic the Diseases, 79:1351.

Correlation of Plasma 14-3-3η Levels with Disease Activity in Methotrexate-Naïve RA Patients Treated with Upadacitinib Monotherapy in the SELECT-EARLY Phase 3 Study

- **Patients**: 200 MTX-naïve RA patients.
- **Timepoints**: Baseline, 2 weeks, and 24 weeks.
- **Treatments**: Upadacitinib (UPA) vs methotrexate.
- **Key Findings**



- At baseline, 79% of patients tested positive for 14-3-3eta, with levels correlating significantly with disease activity measures such as CDAI, DASCRP, and SDAI.
- Changes in 14-3-3eta levels at week 24 in the upadacitinib group correlated positively with improvements in disease activity measures (ΔCDAI, ΔDASCRP, ΔSDAI).

- **Conclusions:** 14-3-3eta levels significantly decrease with upadacitinib treatment in RA patients, and this reduction correlates with improvements in disease activity. These findings highlight the potential of 14-3-3eta as a key biomarker for optimizing treatment strategies in RA management.

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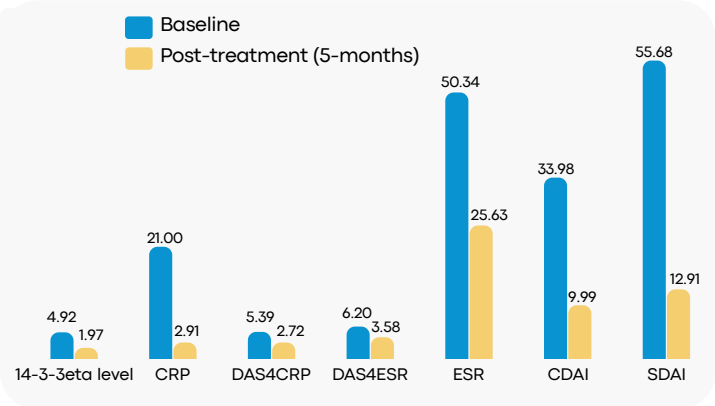
4. Shovman O, Gilburd B, Watad A, et al. (2019) Pharmacological Research, 141:623-626.

Decrease in 14-3-3η Protein Levels Correlated with Improvement in Disease Activity in RA Patients Treated with Tofacitinib

- **Patients**: 35 RA patients.
- **Timepoints**: Baseline and after 5 months of treatment.
- **Treatments**: Tofacitinib (5 mg twice daily).
- **Key Findings**



- 14-3-3eta positivity dropped from 57% to 37% over 5 months, with mean levels decreasing from 4.92 to 1.97 ng/mL. This reduction was accompanied by significant improvements in all disease activity indices (DAS28-ESR, DAS28-CRP, CDAI, and SDAI).
- Decreases in 14-3-3eta levels strongly correlated with improvements in DAS4-ESR (r=0.50, $p < 0.01$) and DAS4-CRP (r=0.46, $p < 0.01$), and ESR (r=0.36, p=0.03), with moderate correlations were seen with CDAI (r=0.32, p=0.065) and SDAI (r=0.33, p=0.051).

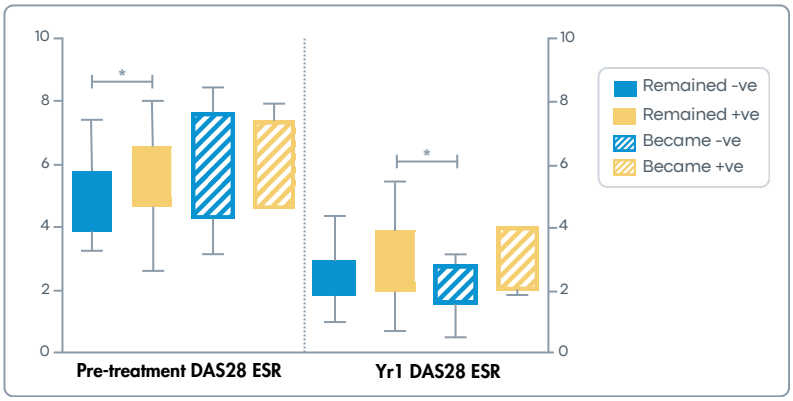
- **Conclusions:** 14-3-3eta is a modifiable biomarker, and its reduction is correlated with improvements in disease activity in RA patients treated with Tofacitinib. This suggests 14-3-3eta may serve as an effective marker for monitoring treatment response in RA.

Clinical assessment scale	Δ14-3-3eta Correlation Coefficient	P value
ΔCRP	0.21	0.23
ΔDAS4CRP	**0.46**	**0.006**
ΔDAS4ESR	**0.50**	**0.002**
ΔESR	**0.36**	**0.03**
ΔCDAI	**0.32**	**0.065**
ΔSDAI	**0.33**	**0.051**

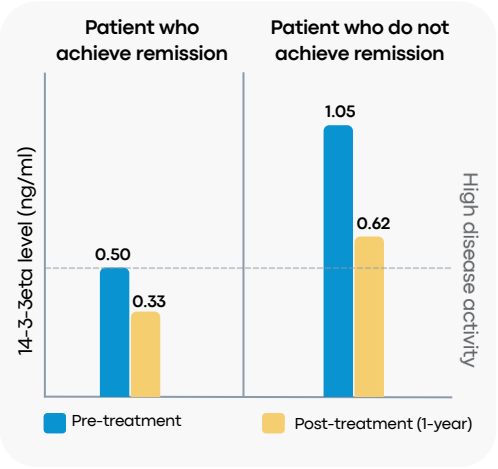
5. Hirata S, Marotta A, Gui Y, et al. (2015). Arthritis Research & Therapy, 17:280.

Serum 14-3-3η Level is Associated with Severity and Clinical Outcomes of Rheumatoid Arthritis, and Its Pretreatment Level is Predictive of DAS28 Remission with Tocilizumab.

- **Patients**: 149 RA patients.
- **Timepoints**: Baseline and 1-year follow-up.
- **Treatments**: Methotrexate, adalimumab, tofacitinib, tocilizumab



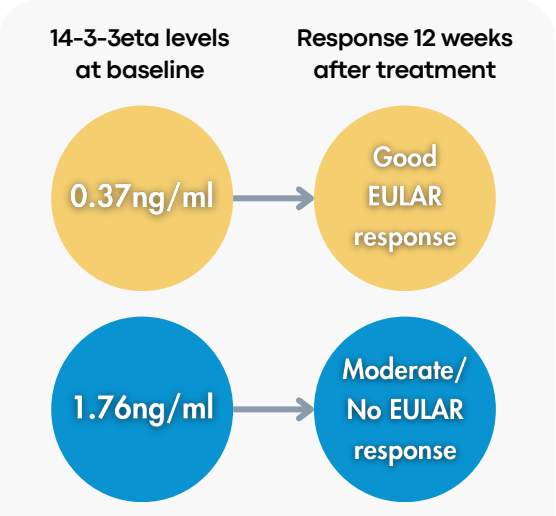
- **Key Findings**
  - Across all treatment classes, 14-3-3eta levels significantly decreased after one year of treatment, particularly in patients achieving better clinical outcomes, indicating that 14-3-3eta is modifiable with treatment.
  - Higher baseline 14-3-3eta levels were associated with more severe disease activity. Patients who became 14-3-3eta negative by one year had lower disease activity (DAS28-ESR) than those who remained positive.
  - Pre-treatment 14-3-3eta levels were an independent predictor of remission in TCZ-treated patients, while other biomarkers, such as CRP, were less informative.
- **Conclusions:** Serum 14-3-3eta is a biomarker for monitoring RA disease activity and predicting treatment response, especially in patients treated with TCZ. Its modifiability over time suggests it could play a key role in ongoing disease management and therapeutic decision-making.



6. Sagawa A, Kaneda M, Gui Y, et al. (2014). Annals of the Rheumatic Diseases, 73:260.

Evaluation of Serum 14-3-3η Levels in a Japanese RA Cohort Treated with Tocilizumab.

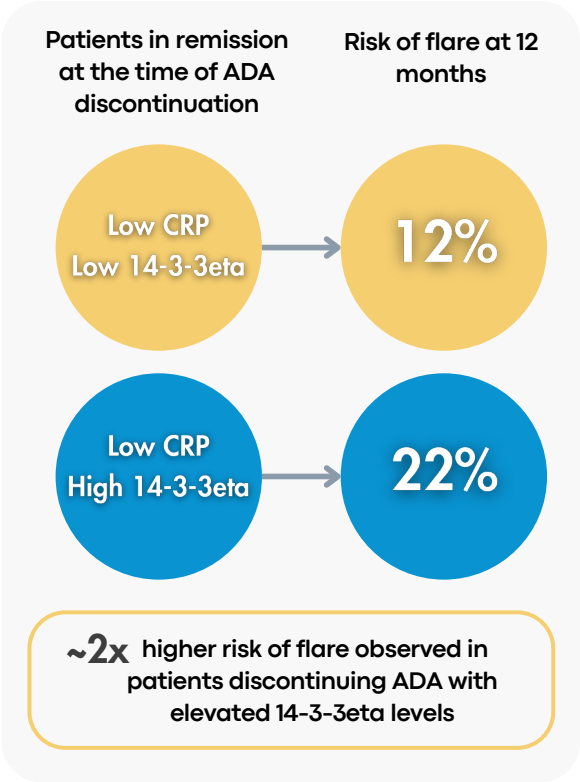
- **Patients**: 41 RA patients.
- **Timepoints**: Baseline and after 12 weeks of tocilizumab (TCZ) treatment.
- **Treatments**: Tocilizumab (8 mg/kg IV every 4 weeks).
- **Key Findings**
  - A significant decrease in 14-3-3eta levels was observed post-treatment, with this reduction also correlating with greater decreases in MMP3 levels, highlighting 14-3-3eta's role in monitoring RA activity.
  - Lower pre-treatment 14-3-3eta levels were linked to better clinical outcomes, including remission, with 14-3-3eta negativity significantly increasing the likelihood of achieving remission (OR 3.4).
- **Conclusions:** Serum 14-3-3eta has the potential for monitoring disease activity and predicting response to tocilizumab in RA patients, with potential to guide treatment strategies.



7. Hirata S, Marotta A, Hanami K, et al. (2017). Annals of the Rheumatic Diseases, 76:791

14-3-3η Predicts Joint Damage Progression and Flaring After Adalimumab Discontinuation

- **Patients**: 62 RA patients.
- **Timepoints**: Baseline, after discontinuation of adalimumab (ADA), and at flare points.
- **Treatments**: Discontinuation of ADA after 1 year.
- **Key Findings**
  - Higher baseline 14-3-3eta levels, and an increase at the time of ADA discontinuation, were significantly associated with elevated Sharp/van der Heijde (SHS) scores at 12 months and during flares, indicating a link to ongoing joint damage despite clinical remission.
  - Patients with low CRP and high 14-3-3eta levels were twice as likely to experience flares within 12 months of discontinuing adalimumab compared to those with low 14-3-3eta (22% vs. 12%).
- **Conclusions:** Baseline 14-3-3eta levels and subsequent increases are associated with worse radiographic outcomes and flares in RA patients after ADA discontinuation. Using 14-3-3eta and CRP together can help predict the risk of flare and guide clinical decisions on discontinuation of biologic therapy.



In treat-to-target strategies aimed at achieving clinical and radiographic remission, higher or rising 14-3-3eta levels may signal the need for tighter treatment control. Patients with lower or decreasing 14-3-3eta levels, especially those reverting to negative, are more likely to achieve better clinical and radiographic outcomes, potentially supporting decisions to reduce treatment intensity.

Publication Overview

Author	Year	Journal	# Patients	Treatments	Timepoints	Takeaway
Carrier N, et al.	2016	Arthritis Research & Therapy	331 early polyarthritis patients	DMARDs, primarily MTX	Baseline,12, 18, 30, 42, 60 months	14-3-3eta levels ≥0.50 ng/ml at baseline and during treatment predict a lower likelihood of SDAI remission and higher radiographic progression, while decreases in 14-3-3eta are associated with better long-term outcomes.
Carrier N, et al.	2020	RMD Open	749 early inflammatory polyarthritis patients	MTX or combination DMARDs	Baseline and annual follow-ups for up to 5 years	Elevated 14-3-3eta levels (≥0.50 ng/mL) indicate an increased risk of REP and can help monitor non-erosive patients at risk for future joint damage, particularly when used alongside CRP levels.
Sornasse T, et al.	2020	Annals of the Rheumatic Diseases	200 MTX-naïve RA patients	Upadacitinib (UPA) vs methotrexate	Baseline, 2 weeks, and 24 weeks	14-3-3eta levels significantly decrease with upadacitinib treatment at 24 weeks in RA patients, correlating with improvements in disease activity.
Shovman O, et al.	2019	Pharmacological Research	35 RA patients	Tofacitinib (5 mg twice daily)	Baseline and after 5 months	14-3-3eta is a modifiable biomarker, with its reduction correlating strongly with improvements in disease activity in RA patients treated with Tofacitinib.
Hirata S, et al.	2015	Arthritis Research & Therapy	149 RA patients	Tocilizumab, MTX, adalimumab, tofacitinib	Baseline and 1-year follow-up	After one year of treatment, 14-3-3eta levels significantly decreased, especially in patients with better clinical outcomes, with higher baseline levels linked to more severe disease and 14-3-3eta negativity associated with lower disease activity.
Sagawa A, et al.	2014	Annals of the Rheumatic Diseases	41 RA patients	Tocilizumab (8 mg/kg IV)	Baseline and after 12 weeks	A decrease in 14-3-3eta levels post-treatment correlates with improved RA activity and better clinical outcomes, with lower pre-treatment levels linked to a higher likelihood of remission.
Hirata S, et al.	2017	Annals of the Rheumatic Diseases	62 RA patients	Discontinuation of adalimumab after 1 year	Baseline, after adalimumab discontinuation, and at flare points	Higher baseline 14-3-3eta levels and increases post-ADA discontinuation are associated with worse radiographic outcomes and a higher risk of flares, especially when combined with low CRP.

14-3-3eta for Rheumatoid Arthritis

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14-3-3eta ASRs are available as an LDT at the following labs:

Quest Diagnostics	
Test Name	**Test Code**
14-3-3eta Protein	91455

Labcorp	
Test Name	**Test Code**
14-3-3eta Protein	504550
RheumAssure® (14-3-3eta, RF, anti-CCP)	504509
RAdx6 Profile (14-3-3eta, RF, anti-CCP, anti-CEP1, anti-Sa, anti-CarP)	520304
SeroNeg RAdx4 Profile (14-3-3eta, anti-CEP1, anti-Sa, anti-CarP)	520305
RA Profile with Reflex to SeroNeg RAdx4 (RF & anti-CCP, reflex to: 14-3-3eta, anti-CEP1, anti-Sa, anti-CarP)	520298

ARUP Laboratories	
Test Name	**Test Code**
14-3-3eta Protein	3017890
Early and Established Rheumatoid Arthritis (RA) Panel (14-3-3eta, RF, anti-CCP)	3017891

COMING SOON

Sonic Healthcare USA	
Divisions	**Test Code**
Clinical Pathology Laboratories	Available Q1 2025
Sunrise Medical Laboratories	Available Q1 2025
East Side Clinical Laboratory	Available Q1 2025
Sonic Reference Laboratory	Available Q1 2025
American Esoteric Laboratories	Available Q1 2025
Pathology Laboratories	Available Q1 2025
Clinical Labs of Hawaii	Available Q1 2025

Partner with Augurex

Join us in improving diagnostic options for RA. Contact us for more information on how to access 14-3-3eta and collaborate to expand testing availability.

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