



Disease Activity Trajectories in Early Rheumatoid Arthritis Under Biologic Therapy

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Abstract

Two patients who meet the same classification criteria for early rheumatoid arthritis on the same day can go on to have almost nothing in common in their disease course once biologic therapy is started, yet the trial literature that established biologic efficacy in early disease was built around single-timepoint endpoints rather than the shape of each patient's disease activity curve over time. This article synthesizes the literature on disease activity trajectories in early rheumatoid arthritis treated with biologic agents, drawing together the measurement infrastructure that makes trajectories comparable across patients (the DAS28, EULAR response criteria, and ACR/EULAR remission and classification criteria), the treat-to-target and window-of-opportunity evidence explaining why early trajectory shape carries independent prognostic weight, the landmark early-RA biologic trials read through a trajectory lens, and the group-based trajectory modeling methodology now applied to real-world cohorts to characterize distinct disease-course subgroups. We give particular attention to predictors that distinguish rapid-remission from persistently active trajectories and to difficult-to-treat rheumatoid arthritis as the clinical phenotype at the persistent-activity end of the spectrum. Read together, the evidence supports early, target-driven, biologic-inclusive therapy as a strategy that shifts trajectories toward faster, deeper, more sustained improvement, while leaving substantial heterogeneity within every treatment arm studied to date, and points toward applying trajectory-modeling methods directly to existing trial data as a clear next step.

Keywords: rheumatoid arthritis; disease activity trajectory; biologic therapy; treat-to-target; group-based trajectory modeling

1. Introduction

Rheumatoid arthritis (RA) is, at diagnosis, a remarkably heterogeneous disease masquerading as a single label. Two patients who both meet the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria on the same morning — the same tender and swollen joint counts, the same acute-phase reactant, the same seropositivity — can go on to have almost nothing in common clinically two years later [1]. One may reach sustained remission within months of starting a conventional synthetic disease-modifying antirheumatic drug (csDMARD) and never need a biologic. Another may cycle through three mechanistically distinct biologic agents and still carry a Disease Activity Score in 28 joints (DAS28) above 5.1 at eighteen months. For decades, the clinical trial literature that established biologic therapy's efficacy in early RA answered a narrower, more tractable question than "what happens to this patient" — it answered "what happens, on average, to a randomized group of patients like this one." Mean DAS28 reduction curves, proportions achieving ACR50, and radiographic progression scores at a single endpoint are the currency of that literature, and they were the right currency for regulatory approval. They are a much weaker currency for the question a rheumatologist actually needs answered at twelve weeks: is *this* patient's trajectory the trajectory of an eventual remitter, or the trajectory of someone who will need a treatment change at six months.

This article synthesizes what the literature says about disease activity trajectories specifically — the shape, over time, of an individual or subgroup's disease course under treatment — in early RA patients started on biologic therapy, and the closely related literature on the measurement tools, treatment strategies, and predictive factors that make trajectory analysis possible and clinically meaningful. Three bodies of work converge on this topic. First, the measurement and classification literature that gave the field a common, validated language for disease activity: the DAS28 itself, the EULAR and ACR/EULAR response and remission criteria built on it, and the 2010 classification criteria that made "early RA" a well-defined entry point for trials in the first place [2,3,4,1]. Second, the treat-to-target and window-of-opportunity literature, which reframed early RA management from a fixed drug sequence into an iterative, target-driven strategy and provided the

theoretical basis for why the *first* months of treatment disproportionately determine the long-run course [5,6,7,8]. Third, and most directly, the landmark early-RA biologic trials — BeSt, PREMIER, COMET, ASPIRE, TEMPO, and U-Act-Early — whose serial disease activity measurements are, in retrospect, trajectory data even though most were analyzed and reported as single-timepoint comparisons, and the more recent literature that has gone back to exactly this kind of longitudinal data with formal trajectory-modeling methods to describe the distinct disease courses hiding inside those trial and registry populations [9,10,11,12,13,14,15].

Our aim is not to re-litigate whether biologics work in early RA — that question was answered convincingly, and repeatedly, by the trials cited above. It is to ask a more granular question: once biologic therapy is started early in the disease course, what do the disease activity curves that patients actually trace out look like, how many distinct shapes do those curves take, what predicts which shape a given patient will follow, and what does the trajectory framework add that a single twelve-month endpoint comparison cannot. We draw on the group-based trajectory modeling methodology that underlies most of the recent quantitative work in this space [16], on cohort studies that have applied it specifically to RA disease activity data [15], and on the predictor and non-response literature that attempts to explain trajectory membership rather than simply describe it [17]. We close with a discussion of difficult-to-treat RA — the clinical phenotype that, in trajectory terms, corresponds to patients whose curves never flatten into remission or low disease activity despite sequential biologic exposure — and the open questions the trajectory literature has not yet resolved [18].

2. Measuring Disease Activity: The Common Language Trajectories Are Built On

Any discussion of disease activity trajectories presupposes a disease activity metric that can be measured repeatedly, on the same scale, across patients and over years. The DAS28, developed by Prevoo and colleagues as a modification of the original Disease Activity Score to use a 28-joint count rather than the more burdensome 44- or 66/68-joint counts, is that metric for the great majority of the trials and cohorts discussed in this article [2]. It combines a tender joint

count, a swollen joint count, an acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein), and a patient global assessment into a single continuous score, and its introduction was itself a methodological advance specifically aimed at making disease activity trackable in ordinary clinical practice and in longitudinal trials, not only in research settings with the time for a full joint examination. Without a score of this kind, "trajectory" would have no shared numeric meaning across cohorts; the entire trajectory-modeling literature discussed later in this article is, in a real sense, downstream of the DAS28's existence.

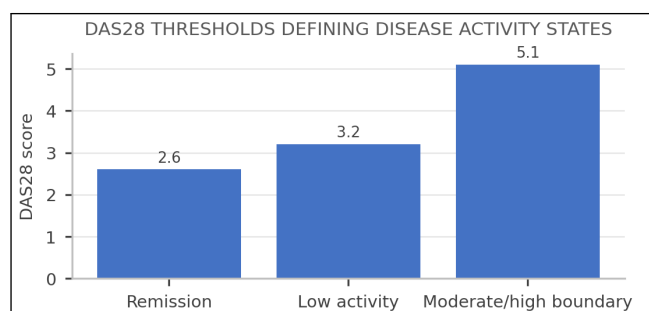


Figure 1: DAS28 disease activity threshold values that define the remission, low-disease-activity, and moderate/high-disease-activity boundaries used throughout the trajectory literature discussed in this article, derived from the original DAS28 validation and EULAR response-criteria work [2,3].

A score is only useful if it can be interpreted, and the EULAR response criteria, validated by van Gestel and colleagues against the ACR and WHO/ILAR response definitions, supplied that interpretation: patients are classified as good, moderate, or non-responders based jointly on the magnitude of DAS28 improvement and the DAS28 level actually reached [3]. This two-dimensional criterion — how much you improved, and where you ended up — is conceptually close to a trajectory in miniature, comparing a starting point and an endpoint, but it is not yet a trajectory in the fuller sense used later in this article, because it collapses everything that happened between baseline and the response-assessment timepoint into a single categorical label. The ACR/EULAR provisional remission definition published by Felson and colleagues pushed the field further toward the kind of fine-grained, repeatable measurement that trajectory modeling needs, offering both a Boolean definition (tender joint count, swollen joint count, C-reactive protein, and patient global assessment each at or below a low threshold) and an index-based Simplified Disease Activity Index threshold, explicitly designed to be stringent enough that

"remission" would mean something close to the absence of detectable inflammatory activity rather than merely low activity [4]. Both the EULAR response criteria and the ACR/EULAR remission definition are, notably, still snapshot definitions; applying them at every visit across a cohort's follow-up, rather than once, is precisely what converts a set of single-timepoint classifications into a trajectory.

The other precondition for a trajectory-based literature on *early* RA specifically is a validated, sufficiently early classification of RA itself. The 2010 ACR/EULAR classification criteria, developed collaboratively by Aletaha, Neogi, Silman, and a large multinational working group, replaced the older 1987 ACR criteria — which were built for and validated against established, often erosive disease — with a score-based algorithm (joint involvement, serology, acute-phase reactants, symptom duration) intended to identify patients with a high probability of developing persistent or erosive disease *before* that damage has already occurred [1]. Every trial synthesized in this article that recruits an "early RA" population is, implicitly or explicitly, relying on some version of this early-identification logic, and the trajectory question this article is centered on — what happens after biologic therapy starts in early disease — could not be posed with much precision without it.

3. Treat-to-Target and the Window of Opportunity: Why Early Trajectories Matter

The treat-to-target (T2T) recommendations, first published by an international task force led by Smolen in 2010 and updated in 2014, articulate the strategic logic that makes trajectory shape, and not just trajectory endpoint, clinically consequential [5,6]. The core recommendation is straightforward to state and demanding to execute: treatment should be aimed at a defined target (remission, or low disease activity when remission is unlikely to be achievable), disease activity should be measured and documented at intervals as frequent as every one to three months for patients with high or moderate disease activity, and therapy should be adjusted whenever there has not been improvement of at least moderate degree within three months or the target has not been reached by six months. This is, functionally, a trajectory-monitoring protocol embedded in clinical guidance years before "trajectory modeling" existed as a named statistical technique applied to RA: the recommendations assume that the

shape of the early response curve, not merely the twelve-month endpoint, carries decision-relevant information, and they operationalize "the curve is flattening in the wrong place" as a trigger for treatment escalation.

The theoretical justification for why the *early* part of that curve matters disproportionately is the window-of-opportunity hypothesis, systematically reviewed by van Nies and colleagues, who examined the accumulated evidence for a time-limited period early in the disease course during which treatment produces disproportionately better long-term outcomes than the same treatment given later [7]. Their review is appropriately measured in its conclusions — evidence for a strict, universally applicable window is more consistent for some outcomes (sustained DMARD-free remission) than others, and the exact boundary of the window is not sharply defined across studies — but the weight of the evidence they synthesize supports the general principle that delay in effective treatment initiation is associated with worse downstream disease course, which is precisely a claim about trajectories: two populations receiving eventually-similar treatment but starting at different points relative to symptom onset are expected, on this hypothesis, to trace out systematically different disease activity curves rather than converging endpoints. The 2007 EULAR recommendations for the management of early arthritis, from a task force led by Combe, formalized the clinical translation of this idea into concrete referral and initiation-of-therapy guidance for the early arthritis clinics that many of the trials and cohorts discussed below were recruited from [8].

Taken together, the T2T framework and the window-of-opportunity evidence explain why the trajectory question this article is organized around is not a statistical curiosity layered onto RA trial data after the fact, but close to the field's own operating logic: clinicians treating early RA are already, in effect, reading each patient's individual trajectory in real time and using its early shape to make escalation decisions, months before the twelve-month primary endpoint that most trials were designed and powered to report.

4. Biologic Therapy Trials in Early RA as (Retrospective) Trajectory Data

The trials that established biologic efficacy in early RA were, almost without exception, designed around a primary endpoint at a single timepoint — typically 52

weeks — even though nearly all of them collected DAS28 or its components at multiple visits along the way. Read with a trajectory lens rather than an endpoint lens, several of these trials already show, in their published figures, that the population-average curve conceals real subgroup heterogeneity.

Table 1: Landmark early-RA biologic trials whose serial disease activity data underlie current trajectory thinking, with the treatment comparison, population, and trajectory-relevant design feature each trial contributes.

Trial	Comparison	Population	Trajectory-relevant design feature
BeSt [9]	Four DAS-steered strategies, incl. initial infliximab or steroid combination	Early, active RA	DAS-driven dose adjustment at fixed intervals; long-term remission and discontinuation follow-up
PREMIER [10]	Adalimumab + MTX vs adalimumab alone vs MTX alone	Early, aggressive RA	Two-year clinical, functional and radiographic follow-up
ERA [19]	Etanercept vs MTX	Early RA, symptom duration under three years	First head-to-head biologic vs csDMARD comparison as initial therapy
COMET [11]	Etanercept + MTX vs MTX alone	Early, active, moderate-to-severe RA	52-week double-blind combination therapy trial
ASPIRE [12]	Infliximab + MTX vs MTX alone	Early RA at high risk of joint damage	Radiographic progression as a co-primary endpoint
TEMPO [13]	Etanercept + MTX vs etanercept alone vs MTX alone	Established RA	Three-arm design isolating the combination therapy effect
OPTIMA [20]	Adalimumab + MTX vs MTX, with later adalimumab withdrawal sub-study	Early RA	Prospective early trajectory checkpoint (week 22) used to trigger a later strategy decision
U-Act-Early [14]	Tocilizumab ± MTX vs MTX-first strategy	Early RA	Sustained-remission strategy trial rather than single-timepoint endpoint

The Dutch BeSt study, led by Goekoop-Ruiterman and colleagues, randomized patients with early, active RA to one of four treatment strategies — sequential monotherapy, step-up combination therapy, initial combination therapy with a tapered high-dose glucocorticoid, or initial combination therapy with infliximab — all managed under a DAS-driven treat-to-target protocol with dose adjustments at fixed intervals. BeSt's own long-term follow-up work, including the analysis by Klarenbeek and colleagues on

discontinuing treatment in patients who reached sustained remission, is itself an explicitly trajectory-oriented piece of literature: rather than reporting a single "percentage in remission at year one," it tracked how many patients could sustain remission after tapering, and, implicitly, who could not, providing some of the earliest systematic evidence that "reached remission" and "sustained a remission trajectory" are different clinical outcomes that a single-timepoint DAS28 comparison cannot distinguish [9].

The PREMIER trial, led by Breedveld and colleagues, compared adalimumab plus methotrexate, adalimumab monotherapy, and methotrexate monotherapy in methotrexate-naïve patients with early, aggressive RA, and reported that combination therapy produced better clinical, functional, and radiographic outcomes than either monotherapy at one and two years [10]. The COMET trial, led by Emery and colleagues, made a similar comparison — etanercept plus methotrexate versus methotrexate alone — in an active, early, moderate-to-severe RA population, again with combination therapy outperforming monotherapy on remission and radiographic non-progression outcomes over 52 weeks [11]. The ASPIRE trial, led by St Clair and colleagues, tested infliximab plus methotrexate against methotrexate alone in early RA specifically selected to be at high risk of joint damage, and likewise found the combination arm produced greater reductions in radiographic progression alongside superior clinical response [12]. The TEMPO trial, led by Klareskog and colleagues, was not restricted to early disease but is one of the most frequently cited trials establishing that etanercept plus methotrexate combination therapy is superior to either agent alone, with a substantially higher proportion of combination-therapy patients showing no radiographic progression [13]. And the ERA trial, led by Bathon and colleagues, was among the first to directly compare etanercept with methotrexate as initial therapy in early RA, establishing that a biologic could outperform an established csDMARD as first-line treatment on both clinical response and radiographic progression measures [19].

The OPTIMA trial, led by Smolen and colleagues, asked a related but distinct trajectory question: among methotrexate-naïve early RA patients who reached stable low disease activity on adalimumab plus methotrexate, what happens to the trajectory if the

biologic is withdrawn, and can early trajectory shape on combination therapy identify which patients are suitable candidates for that withdrawal [20]. The trial found that patients who achieved stable low disease activity by week 22 on combination therapy were substantially more likely to sustain good outcomes after adalimumab withdrawal than patients who had not reached that early target, which is, again, a direct demonstration that the shape of the early on-treatment curve — not simply whether a twelve-month endpoint was eventually reached — carries prognostic information that a strategy trial can act on. OPTIMA's design, deliberately built around an early trajectory checkpoint used to trigger a later strategy decision, is one of the clearest examples in the biologic-trial literature of trajectory-shape information being used prospectively rather than only described retrospectively.

More recently, the U-Act-Early trial, led by Bijlsma and colleagues, tested a different strategic question relevant to trajectories specifically: whether starting tocilizumab (alone or combined with methotrexate) as initial therapy produces a better sustained-remission trajectory than starting methotrexate first and escalating only if needed [14]. The trial's strategy-based design — comparing treatment *sequences* rather than single fixed regimens — is closer in spirit to trajectory thinking than a conventional two-arm efficacy trial, because its primary outcome (sustained remission over a defined window, not remission at a single visit) explicitly rewards a flat, low curve rather than merely a low value at one point in time.

Read as a set, these trials consistently support two claims relevant to trajectories. First, combination therapy (biologic plus methotrexate, or in BeSt's case, an aggressive DAS-driven strategy with early biologic or glucocorticoid support) tends to produce steeper early improvement and a higher proportion of patients reaching a low, stable plateau than monotherapy, which is a statement about curve shape, not only endpoint level. Second, and just as importantly, none of these trials show homogeneous response: in every trial, a meaningful minority of patients on the best-performing arm do not reach the target, and a meaningful minority on the comparator arms do reach it anyway. That residual heterogeneity, visible in every one of these trials' individual-patient data even when it is not the headline result, is exactly what the trajectory-modeling

literature discussed next was built to characterize directly rather than treat as noise around a mean.

5. Group-Based Trajectory Modeling and Its Application to RA

Group-based trajectory modeling (GBTM), the statistical framework most commonly used to formally identify disease activity trajectory subgroups, was developed and is reviewed for a clinical research audience by Nagin and Odgers [16]. The method treats repeated measures on each individual — here, DAS28 or a related composite index at each clinic visit — as arising from a mixture of a small number of latent trajectory groups, each with its own smooth (typically polynomial) mean curve over time, and estimates both the shape of each group's curve and each individual's probability of belonging to it, rather than assuming every patient follows the same population-average curve with individual-level noise around it. Applied to a disease like RA, whose treat-to-target management already anticipates heterogeneous response, GBTM offers something the EULAR response criteria and ACR/EULAR remission definitions cannot by themselves: a data-driven answer to how many meaningfully distinct disease courses exist in a given population and what each one looks like over its full duration, not just at the response-assessment visit.

Movahedi and colleagues applied exactly this approach to a real-world RA cohort, deriving disease activity trajectories separately for early and established RA patients and characterizing the distinct trajectory groups that emerged — patients with disease activity that falls rapidly and stays low, patients whose disease activity falls more gradually to a moderate plateau, and patients whose disease activity remains persistently elevated despite treatment [15]. The value of this kind of analysis over a single treat-to-target endpoint is that it makes the *persistently active* group visible as a distinct, identifiable population rather than an average that gets diluted into a cohort-wide mean DAS28 reduction; a trajectory group with, say, one in six or seven patients in it can be entirely invisible in a headline "mean DAS28 fell by X points" summary statistic while still representing a clinically important, and clinically actionable, subpopulation.

The broader implication of applying GBTM (or related latent-class and mixed-effects trajectory methods) to biologic-treated early RA cohorts is a reframing of the clinical question from "did this population respond to

this drug" to "which trajectory group is this patient tracking toward, and how early in follow-up can that be recognized." That reframing connects directly back to the treat-to-target logic discussed earlier: if a three-month or six-month DAS28 trajectory reliably predicts eventual group membership, then the treat-to-target rule of escalating therapy after inadequate improvement at three months is not merely a reasonable clinical heuristic but a rule that is, in principle, approximating the trajectory-classification decision a formal statistical model would make with more data and more precision.

It is worth being precise about what GBTM assumes and what it does not, because the method is sometimes presented as though it discovers a biologically fixed number of disease subtypes rather than a statistically convenient summary of a continuous underlying phenomenon. Nagin and Odgers are explicit on this point in their methodological review: the latent trajectory groups a GBTM analysis returns are a flexible approximation to what may well be a continuous distribution of individual trajectories, not necessarily evidence for discrete, biologically distinct disease subtypes, and the number of groups a given analysis settles on is itself a modeling choice governed by standard statistical criteria (Bayesian information criterion, average posterior probability of group assignment, and similar diagnostics) rather than a ground truth waiting to be uncovered [16]. This matters for how the RA trajectory literature should be read: when Movahedi and colleagues report, say, three or four trajectory groups in their cohort, the clinically useful content of that finding is the qualitative shape and separation of the curves — a group that resolves quickly, a group that resolves slowly, a group that does not resolve — rather than a claim that exactly that number of biological RA subtypes exists [15]. Two cohorts with genuinely similar underlying response heterogeneity could reasonably be modeled with three groups in one study and five in another without any contradiction, simply because of differences in cohort size, follow-up duration, or the granularity the fitting procedure was allowed to select. Readers translating this literature into clinical intuition should therefore treat "how many trajectory groups" as a secondary, model-dependent detail, and treat "does a persistently-active minority exist that the population mean obscures" as the primary, more robust finding that recurs across studies regardless

of exactly how many groups each analysis happens to report.

6. Predictors of Trajectory Membership and Treatment Response

If trajectory groups are real and clinically distinct, the next question is what predicts which group a given patient will belong to, ideally early enough in the disease course to inform an initial treatment choice rather than only explaining outcomes retrospectively. Teitsma and colleagues addressed a closely related question directly: in patients with new-onset RA started on treat-to-target methotrexate therapy, they developed and validated clinical predictors of an inadequate response, identifying baseline characteristics associated with patients who would go on to need treatment escalation rather than achieving target on methotrexate alone [17]. Work of this kind is the natural complement to the trajectory-modeling literature: where Movahedi and colleagues describe the trajectory groups that exist in an already-treated cohort [15], predictor studies like Teitsma and colleagues' attempt to move that classification earlier, from something observed in retrospect to something anticipated at or shortly after treatment initiation [17].

The epidemiological and mechanistic literature on RA more broadly supplies the candidate predictors this kind of modeling draws on. Van der Woude and van der Helm-van Mil's review of RA epidemiology, risk factors, and disease outcomes lays out the established associations — smoking, anti-citrullinated protein antibody (ACPA) and rheumatoid factor seropositivity, higher baseline disease activity, and delayed treatment initiation among them — that recur across the individual predictor studies applied to specific trial and cohort populations [21]. The two Lancet seminar-style reviews on rheumatoid arthritis, by Scott, Wolfe, and Huizinga, and later by Smolen, Aletaha, and McInnes, synthesize this same predictor landscape alongside the disease's broader pathophysiology and management principles, and both are useful as a single-source map of which baseline factors the field considers most consistently associated with a poor prognostic trajectory: seropositivity, high baseline disease activity and acute-phase reactants, early erosive change, and functional impairment at presentation [22,23]. Aletaha and Smolen's more clinically oriented JAMA review on diagnosis and management covers much of the same

predictor ground but frames it explicitly around treatment decision-making, which is the framing most directly relevant to using predictors to anticipate trajectory membership at the point of initial biologic prescribing rather than after the fact [24].

It is worth being honest about the limits of this predictor literature as it stands. Most individual predictors identified across these studies — seropositivity, baseline DAS28, smoking status — have modest individual effect sizes and imperfect discrimination when used alone; no single baseline variable reliably separates an eventual rapid-remission trajectory from an eventual persistent-activity trajectory with the kind of accuracy that would change a first-line prescribing decision on its own. What the trajectory-modeling and predictor literatures together suggest, more realistically, is that a *combination* of baseline predictors plus early on-treatment trajectory shape (the three-to-six month response curve the treat-to-target recommendations already monitor) provides meaningfully better discrimination than either baseline predictors or a single endpoint measurement alone — which is essentially a restatement, in trajectory-modeling language, of why T2T's core recommendation to monitor and act on the early response curve was the right strategic instinct even before the formal trajectory-modeling tools existed to characterize that curve rigorously [5,16].

7. Difficult-to-Treat RA: The Persistent-Activity Trajectory as a Clinical Phenotype

At the far end of the trajectory spectrum sits a population whose disease activity curve never reaches a low, stable plateau despite sequential exposure to multiple biologic or targeted synthetic DMARDs with different mechanisms of action. The EULAR task force led by Nagy formalized a definition of "difficult-to-treat RA" specifically to give this population — previously described inconsistently across the literature as "refractory," "treatment-resistant," or "multi-drug-failure" RA — a standard, reproducible clinical definition: treatment failure (lack of response, by treat-to-target criteria) of two or more biologic or targeted synthetic DMARDs with different mechanisms of action after failing csDMARD therapy, combined with signs suggestive of active or progressive disease and/or a management perception that symptoms are burdensome to the patient [18].

In trajectory terms, difficult-to-treat RA is the clinical

label for a specific, identifiable trajectory-group signature: not a single flat high-activity curve from the outset, but a curve that shows repeated partial improvements after each new drug initiation, each followed by a plateau or relapse that falls short of the treat-to-target goal, across two or more consecutive drug trials. This pattern is qualitatively different from simple primary non-response to a first biologic, and the Nagy definition's insistence on *multiple* drug failures with *different mechanisms* is, functionally, a requirement that the patient's trajectory has already ruled out drug-specific explanations (a single ineffective mechanism, an immunogenic loss of response to one agent) before the "difficult-to-treat" label is applied. This matters directly for the trajectory-modeling literature discussed above: a GBTM analysis applied naively to a cohort that includes both new starters and multiply-switched difficult-to-treat patients risks conflating two different phenomena — an initial trajectory group that never responds to a first-line biologic, and a distinct, sequential-non-response trajectory that only becomes visible after following a patient through several treatment courses — under a single "persistently high" latent class, when the underlying clinical and, plausibly, biological mechanisms may differ meaningfully between the two.

8. Open Challenges

Several gaps recur across the literature synthesized here. First, and most fundamentally, relatively few of the studies that generate genuinely longitudinal, multi-visit disease activity data — the landmark early-RA biologic trials among them — were analyzed with formal trajectory-modeling methods at the time of their original publication; the trajectory-specific literature that exists, exemplified by work like Movahedi and colleagues', has generally been applied to registry and observational cohort data rather than to the individual-patient data from the major randomized trials themselves, leaving an underexploited opportunity to re-analyze trial data explicitly for trajectory heterogeneity rather than treatment-arm averages [15]. Second, the predictor literature that exists is stronger on identifying statistically significant baseline associations than on producing clinically actionable, prospectively validated discrimination between trajectory groups at the point of initial treatment choice; Teitsma and colleagues' work is a comparatively rare example of a predictor model explicitly developed and validated for this purpose, and

the field would benefit from more studies built to the same standard across different biologic mechanisms rather than treating methotrexate response prediction as a solved template that generalizes automatically [17].

Third, the relationship between the window-of-opportunity hypothesis and trajectory modeling remains under-integrated: van Nies and colleagues' systematic review establishes that delayed treatment initiation is associated with worse long-term outcomes in aggregate, but comparatively little published trajectory-modeling work has directly tested whether time-to-treatment functions as a predictor of *which* trajectory group a patient falls into, as opposed to a predictor of endpoint outcomes more generally [7]. Fourth, difficult-to-treat RA as formally defined by Nagy and colleagues is a recent (2021) construct, and the trajectory-modeling literature has not yet, to our knowledge, been systematically applied to characterize the shape of the difficult-to-treat trajectory itself — whether it is better described as one persistently flat curve, a series of shallow partial-response curves separated by drug switches, or a heterogeneous mixture of both — which would be a natural and clinically valuable extension of the methodology reviewed here [18]. We do not think any of these gaps undermine the core, well-evidenced claims that early, target-driven, often biologic-inclusive therapy shifts the population distribution of disease activity trajectories toward faster, deeper, and more sustained improvement, and that meaningful trajectory heterogeneity persists within every treatment arm studied to date — but they are the honest state of the evidence, and future work claiming to predict individual trajectory membership with clinical-grade accuracy should be read against this backdrop.

9. Conclusion

The literature reviewed here supports treating disease activity trajectory, rather than a single endpoint measurement, as the more clinically faithful unit of analysis for early RA under biologic therapy. The measurement and classification infrastructure that makes this possible — the DAS28, the EULAR response criteria, the ACR/EULAR remission definition, and the 2010 classification criteria — was built incrementally over roughly two decades specifically to allow disease activity to be tracked consistently and repeatedly across patients and over time [2,3,4,1]. The treat-to-target and

window-of-opportunity literature explains why the early shape of that tracked curve, not only its eventual level, carries independent prognostic weight, and gives clinicians a real-time heuristic for reading it [5,6,7]. The landmark early-RA biologic trials, read with a trajectory lens, show consistently that combination and treat-to-target strategies shift the population curve toward faster, deeper improvement while leaving real, persistent heterogeneity in every arm [10,11,12,13,19,14,9]. Formal trajectory-modeling methods, applied so far mostly to observational cohorts rather than trial data, make that heterogeneity explicit and classifiable rather than treating it as noise around a mean [16,15]. And the predictor and difficult-to-treat-RA literatures together sketch, if still incompletely, what distinguishes the patients who will trace a rapid-remission curve from those who will need sequential biologic switches and may ultimately meet formal criteria for a persistently active, difficult-to-treat trajectory [17,21,18]. Bringing these threads together into a single trajectory-oriented account, rather than reading them as separate literatures on measurement, strategy, trials, and prognosis, is, in our view, the most useful synthesis this body of evidence currently supports — and it points toward a clear next step for the field: applying the trajectory-modeling methods now well established in observational RA research directly to the individual-patient data already collected, but not yet analyzed this way, in the major early-RA biologic trials themselves.

For the individual clinician managing an individual patient, the practical upshot of this synthesis is less about any single number and more about a shift in what gets watched and when. A treat-to-target visit at three months is not simply a checkpoint against a fixed DAS28 threshold; read through the trajectory literature, it is an early, noisy but informative sample of a curve whose eventual shape can already be partially anticipated, and whose trajectory group membership becomes more confidently classifiable with each additional data point collected. That reframing does not by itself resolve the open questions catalogued above — it does not tell a clinician, at three months, with certainty, whether a given patient's curve will flatten into remission or persist into a difficult-to-treat course — but it does argue against treating a single early visit's disease activity value in isolation from the trajectory it sits on, and against treating the twelve-month trial endpoint as the only

outcome that matters when the shape of the path to that endpoint, and the population of patients whose paths never reach it, are themselves the clinically and scientifically important findings.

10. References

1. Aletaha, D., Neogi, T., Silman, A.J., Funovits, J., Felson, D.T., Bingham, C.O., et al. (2010) 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis & Rheumatism*, 62(9): 2569-2581. DOI: [10.1002/art.27584](https://doi.org/10.1002/art.27584)
2. Prevoo, M.L.L., van 't Hof, M.A., Kuper, H.H., van Leeuwen, M.A., van de Putte, L.B.A., van Riel, P.L.C.M. (1995) Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis & Rheumatism*, 38(1): 44-48. DOI: [10.1002/art.1780380107](https://doi.org/10.1002/art.1780380107)
3. van Gestel, A.M., Prevoo, M.L.L., van 't Hof, M.A., van Rijswijk, M.H., van de Putte, L.B.A., van Riel, P.L.C.M. (1996) Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. *Arthritis & Rheumatism*, 39(1): 34-40. DOI: [10.1002/art.1780390105](https://doi.org/10.1002/art.1780390105)
4. Felson, D.T., Smolen, J.S., Wells, G., Zhang, B., van Tuyl, L.H.D., Funovits, J., et al. (2011) American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis & Rheumatism*, 63(3): 573-586. DOI: [10.1002/art.30129](https://doi.org/10.1002/art.30129)
5. Smolen, J.S., Aletaha, D., Bijlsma, J.W.J., Breedveld, F.C., Boumpas, D., Burmester, G., et al. (2010) Treating rheumatoid arthritis to target: recommendations of an international task force. *Annals of the Rheumatic Diseases*, 69(4): 631-637. DOI: [10.1136/ard.2009.123919](https://doi.org/10.1136/ard.2009.123919)
6. Smolen, J.S., Breedveld, F.C., Burmester, G.R., Bykerk, V., Dougados, M., Emery, P., et al. (2016) Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Annals of the Rheumatic Diseases*, 75(1): 3-15. DOI: [10.1136/annrheumdis-2015-207524](https://doi.org/10.1136/annrheumdis-2015-207524)
7. van Nies, J.A.B., Krabben, A., Schoones, J.W., Huizinga, T.W.J., Kloppenburg, M., van der Helm-van Mil, A.H.M. (2014) What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Annals of the Rheumatic*

- Diseases, 73(5): 861-870. DOI: [10.1136/annrheumdis-2012-203130](https://doi.org/10.1136/annrheumdis-2012-203130)
8. Combe, B., Landewe, R., Lukas, C., Bolosiu, H.D., Breedveld, F., Dougados, M., et al. (2007) EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Annals of the Rheumatic Diseases*, 66(1): 34-45. DOI: [10.1136/ard.2005.044354](https://doi.org/10.1136/ard.2005.044354)
 9. Klarenbeek, N.B., van der Kooij, S.M., Güler-Yüksel, M., van Groenendael, J.H.L.M., Han, K.H., Kerstens, P.J.S.M., Huizinga, T.W.J., Dijkmans, B.A.C., Allaart, C.F. (2011) Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. *Annals of the Rheumatic Diseases*, 70(2): 315-319. DOI: [10.1136/ard.2010.136556](https://doi.org/10.1136/ard.2010.136556)
 10. Breedveld, F.C., Weisman, M.H., Kavanaugh, A.F., Cohen, S.B., Pavelka, K., van Vollenhoven, R., Sharp, J., Perez, J.L., Spencer-Green, G.T. (2006) The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis & Rheumatism*, 54(1): 26-37. DOI: [10.1002/art.21519](https://doi.org/10.1002/art.21519)
 11. Emery, P., Breedveld, F.C., Hall, S., Durez, P., Chang, D.J., Robertson, D., Singh, A., Pedersen, R.D., Koenig, A.S., Freundlich, B. (2008) Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet*, 372(9636): 375-382. DOI: [10.1016/S0140-6736\(08\)61000-4](https://doi.org/10.1016/S0140-6736(08)61000-4)
 12. St Clair, E.W., van der Heijde, D.M.F.M., Smolen, J.S., Maini, R.N., Bathon, J.M., Emery, P., Keystone, E., Schiff, M., Kalden, J.R., Wang, B., DeWoody, K., Weiss, R., Baker, D. (2004) Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis & Rheumatism*, 50(11): 3432-3443. DOI: [10.1002/art.20568](https://doi.org/10.1002/art.20568)
 13. Klareskog, L., van der Heijde, D., de Jager, J.P., Gough, A., Kalden, J., Malaise, M., Martín Mola, E., Pavelka, K., Sany, J., Settas, L., Wajdula, J., Pedersen, R., Fatenejad, S., Sanda, M. (2004) Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet*, 363(9410): 675-681. DOI: [10.1016/S0140-6736\(04\)15640-7](https://doi.org/10.1016/S0140-6736(04)15640-7)
 14. Bijlsma, J.W.J., Welsing, P.M.J., Woodworth, T.G., Middelink, L.M., Pethö-Schramm, A., Bernasconi, C., et al. (2016) Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. *Lancet*, 388(10042): 343-355. DOI: [10.1016/S0140-6736\(16\)30363-4](https://doi.org/10.1016/S0140-6736(16)30363-4)
 15. Movahedi, M., Cesta, A., Li, X., Bombardier, C. (2022) Disease activity trajectories for early and established rheumatoid arthritis: real-world data from a rheumatoid arthritis cohort. *PLoS ONE*, 17(9): e0274264. DOI: [10.1371/journal.pone.0274264](https://doi.org/10.1371/journal.pone.0274264)
 16. Nagin, D.S., Odgers, C.L. (2010) Group-based trajectory modeling in clinical research. *Annual Review of Clinical Psychology*, 6(1): 109-138. DOI: [10.1146/annurev.clinpsy.121208.131413](https://doi.org/10.1146/annurev.clinpsy.121208.131413)
 17. Teitsma, X.M., Jacobs, J.W.G., Welsing, P.M.J., de Jong, P.H.P., Hazes, J.M.W., Weel, A.E.A.M., Pethö-Schramm, A., Borm, M.E.A., van Laar, J.M., Lafeber, F.P.J.G., Bijlsma, J.W.J. (2018) Inadequate response to treat-to-target methotrexate therapy in patients with new-onset rheumatoid arthritis: development and validation of clinical predictors. *Annals of the Rheumatic Diseases*, 77(9): 1261-1267. DOI: [10.1136/annrheumdis-2018-213035](https://doi.org/10.1136/annrheumdis-2018-213035)
 18. Nagy, G., Roodenrijs, N.M.T., Welsing, P.M.J., Kedves, M., Hamar, A., van der Goes, M.C., et al. (2021) EULAR definition of difficult-to-treat rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 80(1): 31-35. DOI: [10.1136/annrheumdis-2020-217344](https://doi.org/10.1136/annrheumdis-2020-217344)
 19. Bathon, J.M., Martin, R.W., Fleischmann, R.M., Tesser, J.R., Schiff, M.H., Keystone, E.C., Genovese, M.C., Wasko, M.C., Moreland, L.W., Weaver, A.L., Markenson, J., Finck, B.K. (2000) A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *New England Journal of Medicine*, 343(22): 1586-1593. DOI: [10.1056/NEJM200011303432201](https://doi.org/10.1056/NEJM200011303432201)
 20. Smolen, J.S., Emery, P., Fleischmann, R., van Vollenhoven, R.F., Pavelka, K., Durez, P., Guérette, B., Kupper, H., Redden, L., Arora, V., Kavanaugh, A. (2014) Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet*, 383(9914): 321-332. DOI: [10.1016/S0140-6736\(13\)61751-1](https://doi.org/10.1016/S0140-6736(13)61751-1)
 21. van der Woude, D., van der Helm-van Mil, A.H.M. (2018) Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. *Best Practice & Research Clinical Rheumatology*, 32(2): 174-187. DOI: [10.1016/j.berh.2018.10.005](https://doi.org/10.1016/j.berh.2018.10.005)
 22. Scott, D.L., Wolfe, F., Huizinga, T.W.J. (2010) Rheumatoid arthritis. *Lancet*, 376(9746): 1094-1108. DOI: [10.1016/S0140-6736\(10\)60826-4](https://doi.org/10.1016/S0140-6736(10)60826-4)

23. Smolen, J.S., Aletaha, D., McInnes, I.B. (2016) Rheumatoid arthritis. *Lancet*, 388(10055): 2023-2038. DOI: [10.1016/S0140-6736\(16\)30173-8](https://doi.org/10.1016/S0140-6736(16)30173-8)
24. Aletaha, D., Smolen, J.S. (2018) Diagnosis and management of rheumatoid arthritis: a review. *JAMA*, 320(13): 1360-1372. DOI: [10.1001/jama.2018.13103](https://doi.org/10.1001/jama.2018.13103)

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Not applicable. As a review of previously published literature, this work did not involve human participants, animal subjects, or new primary data collection, and did not require ethical committee approval.

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