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REVIEW

Goals for rheumatoid arthritis: treating to target or treating to prevent?

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Min Yang
Mingyang Guo

Rheumatology Center, PLA General Hospital of Chengdu Military Area Command, Chengdu, Sichuan Province, PR China

Although treat-to-target goals for rheumatoid arthritis (RA) have been well-established through several guidelines in recent years, concerns regarding treat-to-prevent goals for RA remain unclear. RA patients are typically subjected to over- or under-treatment because it is difficult for clinicians to determine the prognosis of RA patients. This typically results in failure to select and identify patient subsets that should receive monotherapy or combination therapy to treat early RA. Understanding treat-to-prevent goals, as well as unfavorable prognoses, risk factors, and prediction methods for RA, is therefore critical for making treatment decisions. Rapid radiographic progression plays a central role in contributing to other composite RA indices, so this may be the best method for defining treat-to-prevent goals for RA. Accordingly, risk factors of rapid radiographic progression have been defined and two prediction models were retrospectively derived based on clinical trial data. Additional studies are required to develop risk models that can be used for accurate predictions.

Keywords: rapid radiographic progression, prognosis, risk factors, prediction models

Introduction

Doctors experience significant difficulty in choosing between monotherapy and combination therapy for treating early rheumatoid arthritis (RA) patients. Several studies have suggested that combination therapy with conventional disease-modifying antirheumatic drugs (DMARDs) and novel biologic agents may be effective during early stages of the disease and may influence the long-term prognosis; however, some early RA patients may achieve clinical remission through the use of a single DMARD.[1,2] Accordingly, this subset of RA patients may be over-treated with the use of combination DMARDs, while other patients may achieve poor treatment response with a single drug. Therefore, selecting and identifying patient subsets to receive monotherapy or combination therapy is critical for properly treating early RA. During the 75th Annual Scientific Meeting of the American College of Rheumatology (ACR), several concerns regarding the 2012 ACR recommendations for treating RA were discussed. Similar to the 2008 ACR recommendations,[3] prognostic assessment of RA was emphasized as a necessary precondition for treatment decisions. The use of monotherapy or combination therapy should be recommended depending upon predictions to determine whether RA patients have a favorable or unfavorable prognosis.

Thus, guidelines should be set that can be used to determine whether the prognosis is favorable or unfavorable. Currently, no guidelines exist to differentiate between poor outcomes and good outcomes for RA treatment.[4] Although various clinical composite indices such as the disease activity score, disease activity score in 28 joints, simplified

Correspondence: Min Yang
Rheumatology Center, PLA General Hospital of Chengdu Military Area Command, Chengdu,
Sichuan Province, PR China
Tel +86 028 865 711 07
Fax +86 028 865 711 07
Email translie@live.cn

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disease activity index (SDAI), clinical disease activity index, health assessment questionnaire, modified health assessment questionnaire, multidimensional health assessment questionnaire, and routine assessment of patient index data, are widely used in clinical practice, these indices are often only useful for evaluating disease activity but not for describing treatment outcomes.[5]

Additionally, risk factors for poor treatment outcomes are not well-defined. Various environment, patient, and disease-associated predictive factors have been proposed for both early and late RA, but their usefulness in guiding treatment choices at the individual level remains unclear. It remains difficult for rheumatology doctors to translate predictions into treatment choices for individual patients recently diagnosed with RA. Additional concerns include effective prediction of treatment outcomes, the usefulness of risk factors, and making treatment decisions based on currently existing evidence. The answers to these questions remain unclear.

Treat-to-target goals versus treat-to-prevent goals

Generally, a good outcome for a disease is considered total recovery or clinical remission. Since total recovery from RA is not possible, clinical remission is considered a good outcome or a treat-to-target goal.[6] Threshold score for clinical remission were clearly defined in the disease activity score (<1.6), disease activity score in 28 joints (<2.6), SDAI (<3.3), clinical disease activity index (<2.8), health assessment questionnaire (≤0.5), modified health assessment questionnaire (≤3.0), multidimensional health assessment questionnaire (≤3.0), and routine assessment of patient index data (≤3.0).[5,7] Furthermore, recently published recommendations established by the ACR and the European League Against Rheumatism define clinical remission of RA as tender joint count, swollen joint count (SJC), C-reactive protein (CRP, mg/dL), and patient global assessment (on a 0–10 scale) all of ≤1 or and SDAI of ≤3.3.[8] These definitions are clinically practicable and widely accepted as treat-to-target goals for RA; however, definitions of poor treatment outcomes or treat-to-prevent goals are vague. Though low, moderate, and high disease activity have been described in some of these composite indices, these activities may not be appropriate for use as prevention goals. Treatment of RA guided by these composite indices is not sufficient for achieving clinical and radiological remission.[9] Furthermore, varying levels of disease activity may not necessarily be a poor treatment outcome for RA. For example, moderate RA activity may be considered a treatment failure if baseline disease activity was low, while treatment may be defined as successful if baseline RA activity was high. Contradictions arise for these multichotomous dependent variables because disease states are described at single time points while disease changes are not described. Thus, treatment outcome should be defined in reference to the level of improvement or deterioration. ACR response criteria (ACR 20, ACR 50, and ACR 70), another composite index, describe the percentage of disease improvement and compare disease activity at two discrete time points; however, these criteria are used to discriminate effective treatment from placebo treatment based on clinical trial data and are not directly applicable to clinical practice.[10]

Thus, treat-to-prevent goal of early RA must be defined. Additionally, disease conditions that should actively be prevented may include death, systemic features, pains, red swelling, joint deformation, and limb disability. Because RA itself is not a fatal disease, it is not reasonable to define treat-to-prevent goals of early RA as death. In clinical practice, prevention of death is not considered a primary goal when treating RA. Moreover, reduction of pain, red swelling, or systemic features does not necessarily indicate the disease has been effectively controlled.

From a clinical perspective, joint deformation, ankylosis, and limb disability are unfavorable outcomes for most early

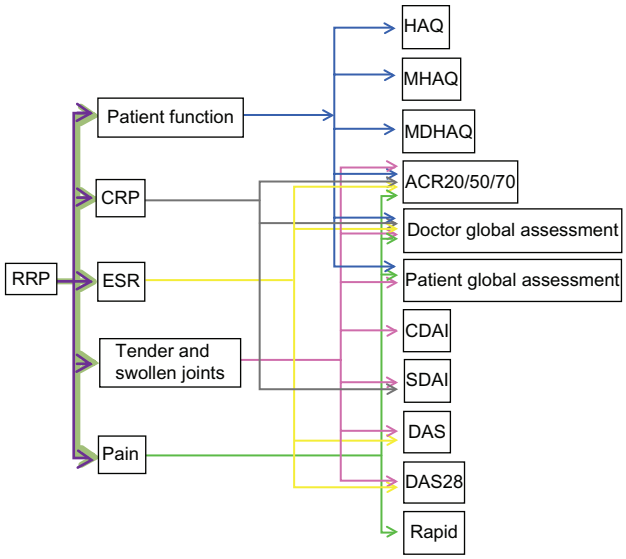

Figure 1 RRP plays a centre role in contributing to other composite RA indices. Because of bone and cartilage erosion and destruction, RRP usually causes severe pains, joint tenderness, swelling, elevated CRP titer and ESR, which weigh heavily in determining several indices of RA, like ACR response criteria, DAS and DAS28, CDAI, SDAI, HAQ and MHAQ, RAPID and MDHAQ.

Abbreviations: RRP, rapid radiographic progression; RA, rheumatoid arthritis; CRP, C response protein; ESR, erythrocyte sedimentation rate; ACR, American College of Rheumatology; SJC, swollen joint count; CDAI, clinical disease activity index; SDAI, simplified disease activity index; HAQ, health health assessment questionnaire; MHAQ, modified health assessment questionnaire; MDHAQ, multidimensional health assessment questionnaire; RAPID, routine assessment of patient index data.

RA patients not receiving drugs or in those receiving DMARD monotherapy. The pathological nature of lesions involving bone and cartilage erosion and destruction eventually results in joint narrowing and fusion.[4] Iconography is a descriptive method used to record these pathological changes.[11] The Sharp/van der Heijde score (SHS), an iconography rating system, was shown to be closely associated with joint deformation and limb disability; and over a period of time (typically 1 year), a rapid increase in the SHS predicts a high probability of disability.[12] Accordingly, a novel index, rapid radiographic progression (RRP), was defined as SHS $\geq$ 5 U/1 year.[13] RRP is typically accompanied by severe pain, joint swelling and tenderness, high titer CRP and elevated erythrocyte sedimentation rate (ESR), which contribute significantly to RA composite indices (Figure 1). Therefore, RRP plays a central role in contributing to other composite RA indices.

In clinical practice, RRP typically occurs in a minority of treated patients; effective therapy in these patients can reduce the odds of progression by up to 78%. Furthermore, early and intensive treatment can slow the rate of radiographic progression.[14] Identifying individual RA patients at high risk for RRP is therefore critical to making appropriate treatment choices.[13] RRP directly indicates a poor outcome for RA patients; thus, it may be the most appropriate marker for defining treat-to-prevent goals for RA.

Risk factors for RRP

Previous studies have indicated that several conditions are associated with unfavorable prognosis of RA (Table 1). Human leukocyte antigen-DRB1[15–17] and protein tyrosine phosphatase nonreceptor 22 genes,[18–20] anti-citrullinated protein antibodies (ACPA),[21–27] ESR,[28,29] CRP,[30,31] rheumatoid factor (RF),[32] and erosion score[33] are well-established risk factors associated with an unfavorable prognosis of RA, while other conditions, such as smoking,[34–36] female sex,[37–39] old age,[40,41] psychological factors,[42] and low level of formal education[43] show inconsistent associations with RA prognosis. Clearly, the definition of an unfavorable prognosis is vague and therefore cannot be interpreted as RRP. Thus, whether these conditions are associated with RRP is unknown.

With the data from an active-controlled study known as Patients Receiving Infliximab (IFX) for the Treatment of RA of Early Onset performed by St Clair et al,[13] this question was partially answered. This double-blind study involved 1049 early RA patients randomly assigned to receive methotrexate (MTX) monotherapy or MTX in combination with IFX over 46 weeks to establish a correlation between RRP and baseline risk factors, including CRP, ESR, SJC, and RF. In these 1049 patients, high titer CRP, RF, and high ESR and SJC are typically suggestive of a high percentage of RRP. Another study reported a similar correlation between CRP, RF, ACPA, erosion score, and RRP.[48] In these two studies CRP, ESR, RF, SJC, ACPA, erosion score, and treatment methods were considered baseline risk factors for predicting the potential for RRP. Additionally, different treatment (monotherapy of MTX and combination therapy of MTX plus IFX) significantly influenced RRP rate. Conservative treatment (monotherapy) typically resulted in a higher RRP rate, while aggressive treatment (combination therapy) remarkably decreased RRP rate. A close correlation between clearly defined risk factors and clearly defined poor outcomes for RA was established. Developing a method for prognostic prediction of RA is now possible.

Risk models

One risk model was derived based on trichotomous variables, including CRP ($<$0.6, 0.6–3 or $>$3 mg/dL), ESR ($<$21, 21–50 or $>$50 mm/h), RF ($<$80, 80–200 or $>$200 U/mL), SJC ($<$10, 10–17 or $>$17), and treatment method.[13] These variables of different levels define a series of subgroups in the 1049 early RA patients. RRP rate in each subgroup reveals the likelihood of RRP in an RA in this subgroup. A similar model derived by Visser et al was based on CRP, RF, ACPA, and erosion score.[48] This risk model was established based on data from a smaller population of 465 RA patients. Clearly in both risk models, the number of subjects in each subgroup is not sufficient to achieve a representative RRP rate. Additionally, CRP level in both models is significantly different, suggesting a large difference between these two early RA populations. Therefore, larger studies need to be conducted to obtain epidemiological data from early RA patients under monotherapy or combination therapy; this will help to establish a more powerful risk model for predicting RA outcomes.

Conclusion

The cause of RA is unknown and the prognosis is not easy to predict. Although several composite indices have been well-defined for predicting a good prognosis, treat-to-target goals for RA, the definition, and risk factors for poor prognosis are unclear. RRP plays a central role in contributing to most composite RA indices and directly reflects poor outcomes of RA; Thus, RRP may be the most suitable marker for defining the treat-to-prevent goals. Identifying individual RA patients

Table 1 Risk factors for unfavorable prognosis of rheumatoid arthritis

Source	Risk factors	Description	OR	95% CI	Predictive value (%)	Reliable[a]	Independent[b]	Simple[c]	Accurate[d]	Well-studied[e]
Papadopoulos et al[15]	HLA-DRBI genes	Causing radiographic erosions in a dose-dependent manner	2.0	1.8–2.2	NA	1	1	0	1	1
Hinks et al[18]	PTPN22 gene	Being associated with more severe and erosive disease	1.9	1.5–2.4	NA	1	1	0	1	1
Hayem et al[44]	Anti-Sa	A sensitive serologic marker for RA patients with severe radiographic damage	NA	NA	75	1	1	0	1	0
Nyhall-Wahlin Bm Fau et al[45]	Smoking	Being associated with the development of severe extra-articular RA	2.3	1.4–3.5	NA	0	0	1	0	1
Camacho et al[40]	Old age	Being associated with an increasingly steep trajectory of disability progression	NA	NA	NA	0	0	1	0	0
Iikuni et al[37]	Female sex	Being prone to greater and faster progression of disability than male	NA	NA	NA	0	0	1	1	0
Lorish et al[42]	Psychological factors	Playing a role in the development of physical disability	NA	NA	NA	0	0	0	0	0
Theodore et al[43]	Low level of formal education	A marker for increased mortality and morbidity	NA	NA	NA	0	0	1	0	0
Van Leeuwen et al[46]	SJC	Being the most appropriate for the prediction of radiological outcome	NA	NA	NA	0	1	1	1	0
Kunihiro et al[21]	ACPA	Predicting erosive changes	2.5	1.0–6.1	NA	1	1	1	1	1
Natacha et al[28]	ESR	Best predictive factors of 10-year radiographic outcome in early RA	2.6	1.2–5.4	NA	1	1	1	1	1
Salaffi et al[30]	CRP	Affecting subsequent progression of radiographic damage in early RA	NA	NA	NA	1	1	1	1	1
Dixey et al[33]	RF	Risk factors for 3-year radiological outcome	NA	NA	67	1	1	1	1	1
Dixey et al[33]	Erosion score	Predicting joint damage progression	NA	NA	90	0	1	1	1	1
Kaye et al[47]	Rheumatoid nodules	Sign of less favorable prognosis than those without nodules	NA	NA	NA	1	1	1	1	1

Notes: [a]Being reproducible, specific, and sensitive; risk factors being inconsistently reported were considered as not reliable; [b]being independent with other risk factors; [c]being easily available and within the expertise and budget of the average practice; [d]being of a degree of accuracy as a marker to guide therapy; [e]being subjected to rigorous comparison with current and accepted practice. 1 = yes and 0 = no.

Abbreviations: ACPA, anti-citrullinated protein antibodies; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; NA, not available; OR, odds ratio; PTPN22, protein tyrosine phosphatase nonreceptor 22; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count.

at a high risk of RRP is therefore critical to making appropriate treatment decisions. Several risk factors have been described to be closely associated with RRP. Some risk models use these risk factors to predict the probability of RRP; however, these risk models were developed retrospectively. Therefore, additional studies are necessary to develop more powerful risk models.

Disclosure

The author reports no conflicts of interest in this work.

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