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Professor Special Lecture: 151st Regular Meeting of the Medical Society of Toho University

Review Article

Concept, Assessment, and Management of Disease Activity in Rheumatoid Arthritis

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ABSTRACT: As a concept, disease activity should be time-differentiated organ damage, and high disease activity should be associated with the high-speed progression of organ damage, mainly joint destruction in rheumatoid arthritis. This concept has been validated by the retrospective analyses of joint destruction during given periods: time-integrated disease activity correlated well with joint destruction. A mathematical description of disease activity as time-differentiated organ damage indicated a new concept, "negative activity," which means the improvement of organ damage, and it should be clearly distinguished from "zero activity," which means neither worsening nor improvement of organ damage. However, current composite activity measures do not distinguish "negative activity" from "zero activity," and the correlation of the time-integrated disease activity score to joint destruction during a given period is considerably insufficient. A formula with the modification of Newton's motion equation indicated the difference between synthetic compounds and biological agents in the importance of patient "capacity." Thus, the primary objective of the serum trough monitoring of biological agents is to avoid the lack of effectiveness due to underdosing, whereas that of synthetic compounds is to avoid dose-dependent adverse events due to overdosing.

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KEYWORDS: activity, damage, joint destruction, rheumatoid arthritis

Introduction

Recent advances in the treatment strategy for rheumatoid arthritis (RA) called "treat to target (T2T)"[1] and the development of biological agents targeting key cytokines such as tumor necrosis factor (TNF) and interleukin-6 have led to favorable outcomes in the majority of Japanese patients with RA[2]; even clinical remission was achieved by 50% of patients.[3] However, pitfalls in the current assessment of the clinical disease activity of RA have been elucidated using high-sensitivity imaging methods such as musculoskeletal ultrasonography (US).[4] Therefore, we provide a constructive view of the concept, assessment, and management of disease activity in RA for

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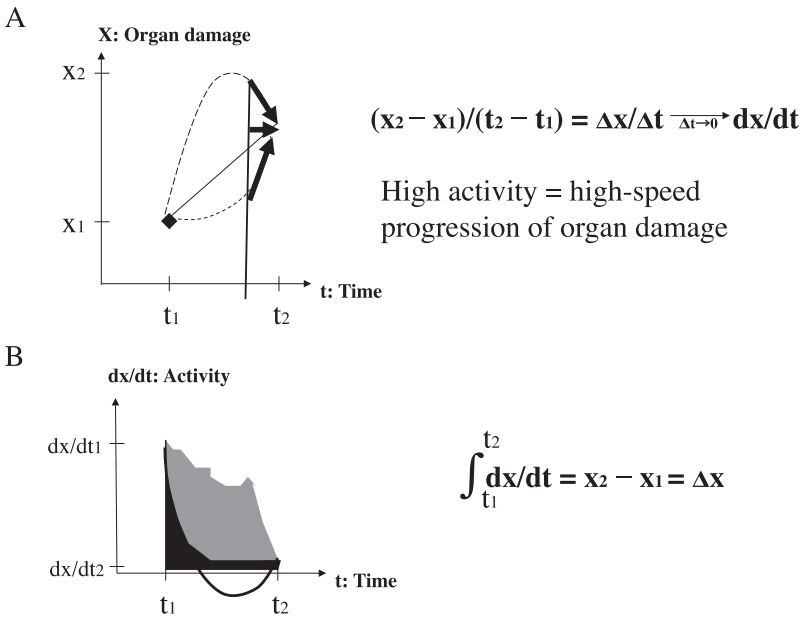

Fig. 1 Concept of disease activity and its temporal relationship with organ damage.
A. Disease activity as time-differentiated organ damage.
Although the speed of organ damage may be constant (solid straight line) or changing (dotted curves) from t_1 to t_2, it can be estimated as constant in a very short time interval. The three arrows indicate negative, zero, and positive activity in order from the top.
B. Organ damage as time-integrated disease activity.
The area under the curve of temporal change in disease activity corresponds to organ damage during the time from t_1 to t_2. Even if the disease activities at times of both t_1 and t_2 are comparable, rapid control of disease activity results in minimal organ damage (area in black), which is much less (the difference shown in gray) than the delayed control of disease activity.

further improvement in the outcome of patients with RA.

Concept of Disease Activity in RA

Because RA is a systemic inflammatory disease predominantly involving the joint synovium, it is hard to precisely assess disease activity. As a concept, disease activity should be time-differentiated organ damage (Fig. 1). Therefore, high disease activity implies the high-speed progression of organ damage, mainly joint destruction in RA. This concept has been validated by the retrospective analyses of joint destruction during given periods: time-integrated disease activity correlated well with joint destruction.[5–10] Indeed, these observations led to the T2T strategy to minimize organ damage such as joint destruction by achieving acceptable disease activity, remission or at least low disease activity, as early as possible.[1]

A mathematical description of disease activity as time-differentiated organ damage indicated a new concept, "negative activity" (Fig. 1). The conventional concept of disease activity included only "zero activity" and "positive activity," and remission included "zero activity" and a clinically nonsignificant "positive activity." However, "zero activity" means neither worsening nor improvement of organ damage, which should be clearly distinguished from "negative activity," which means the improvement of organ damage. Indeed, a considerable number of patients have shown the repair of joint damage as a whole in recent clinical trials. Therefore, a new T2T strategy should aim at the prevention or repair of organ damage as much as possible by achieving "negative or zero activity" according to the existence of organ damage at the start of RA treatment.

Assessment of Disease Activity in RA

The validity of the clinical assessment of RA is determined from various aspects: face validity, content validity,

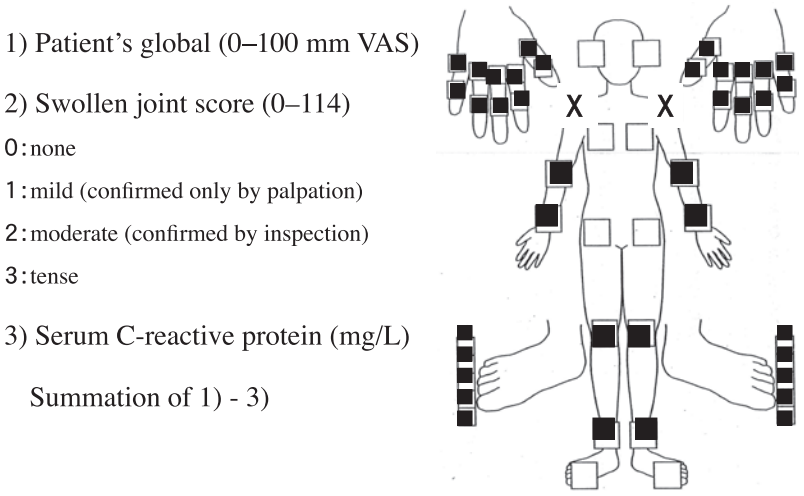

Fig. 2 Handy rheumatoid activity score with 38 joints (HRAS38). HRAS38 is the sum of the patient's global assessment (0-100 mm visual analogue scale (VAS)), swollen joint score of 38 joints (0-3 for each), and serum C-reactive protein level (mg/dL).

Table 1 Comparison between synthetic compounds and biological agents.

	Synthetic compounds	Biological agents
Molecular weight	<10,000 (MTX 454.4; tofactinib citrate 504.5)	>10,000 (IgG ～ 150,000)
Cellular localization of the targeted molecule	Intracellular	Extracellular/cellular membrane
Specificity	Insufficient	Sufficient
Dose	Limited dose	Sufficient dose

MTX: methotrexate.

construct validity, criterion validity, and discriminant validity.[11, 12] As a practical reason, clinical assessment should be feasible.[12] According to the above criteria, composite disease activity measures have been developed and validated in clinical trials. These include DAS (disease activity score),[13] DAS28 (28-joint count DAS),[14] and SDAI (simplified disease activity index).[15] Although all the above composite activity measures include tender joint count and global assessment by the patient, these parameters have been reported to be poorly correlated with joint destruction evaluated by hand and foot radiographs.[16, 17] Previously, we developed a new composite RA activity measure, handy rheumatoid activity score with 38 joints (HRAS38), composed of global assessment by the patient, swollen joint score, and serum C-reactive protein level (Fig. 2).[18] HRAS38 has been validated in 2 clinical trials conducted in Japan[19, 20]; however, it failed to show major advantages over conventional activity measures (unpublished data and our publication[21]). Because we have recently shown again that tender joint count should be excluded from the composite activity measure of RA in a study using joint US as a gold standard,[4] further improvement in the composite activity measure of RA is awaited.

Management of Disease Activity in RA

Because inflammatory disease activity is defined as time-differentiated organ damage, namely, the speed of progression of organ damage, the control of disease activity mimics the brake of an automobile. Deceleration of the speed of organ destruction aiming at "negative or zero activity" can be described as a formula with the modification of Newton's motion equation:

$$F = C \cdot (-d^2x/dt^2)$$

where F is the intensity of treatment (ex. dosage), C is the capacity of the patient (ex. body mass, age, renal function), and $-d^2x/dt^2$ is the deceleration rate of disease activity (x: organ damage; t: time).

The above formula indicates the difference in the importance of "capacity" between synthetic compounds and biological agents. Most of the synthetic compounds with low molecular weights around 500 can easily penetrate the cellular membrane and bind to intracellular molecular targets (Table 1). Their binding to the targeted molecule is not specific enough, which results in the elicitation of various off-target effects and consequently limits the administration dose. Therefore, the available dose variation of synthetic compounds is within several-fold in clinical practice except for glucocorticoids.

On the contrary, biological agents, typically immunoglobulin G antibodies with a molecular weight of ～ 150,000, are unable to penetrate the cellular membrane and only bind to the extracellular or membrane molecular targets. Also, their binding to the targeted molecule is highly specific. Therefore, biological agents can be dose-escalated until the sufficient neutralization of targeted molecules such as TNF.[22] The serum trough level of biological agents correlates with the sufficiency of the neutralization of targeted molecules. Thus, monitoring the serum trough level of biological agents will be widely performed in the near future. It should be noted that the primary objective of the serum trough monitoring of biological agents is to avoid the lack of effectiveness due to underdosing, whereas that of synthetic compounds is to avoid dose-dependent adverse events due to overdosing.

Conclusion

A fundamental understanding of the concept of disease activity as time-differentiated organ damage, mainly joint destruction, is crucial for the management of RA, and it may help the future development of more valid and suitable clinical measures of RA activity than those currently available.

Conflicts of interest: Non declared.

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Specialty Certification

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Auditor of the Japanese Society of Inflammation and Regeneration
Councilor of the Japan College of Rheumatology
Councilor of the Japanese Society of Internal Medicine
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