Mod Rheumatol (2013) 23:1–7
DOI 10.1007/s10165-012-0702-1

REVIEW ARTICLE

Management of rheumatoid arthritis: the 2012 perspective

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Received: 9 April 2012 / Accepted: 11 June 2012 / Published online: 7 July 2012

Abstract Management of rheumatoid arthritis (RA) has improved over the last 10 years. These changes have been monitored in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort, and clinical remission has become a realistic goal. However, we should recognize that the ultimate goal of treatment is to improve long-term outcomes. These improvements have been achieved not only by new drugs, but also by the overall approach toward treating patients. Biologics in RA have been successful; however, safety concerns and pharmacoeconomical issues are still debated. Protein kinase inhibitors have been developed, and can be called "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs." In comparison with biologics, oral MTARDs should be less expensive; however, their safety profile should be confirmed. Considering the limitations of randomized trials, it is encouraged to conduct studies based on daily practice. It is time to consider the application of the evidence generated from "our" patients to patients in daily practice, namely institute-based medicine as opposed to evidence-based medicine, of which "IORRA-based medicine" would be representative. Finally, there remains much for us rheumatologists to do for our patients, including patient-perspective approaches.

Keywords Outcome · Observational cohort · Biologics · MTARDs · Patient perspective

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What have we achieved since 2000?

The readers of *Modern Rheumatology* know that, over the last 10 years, care of patients with rheumatoid arthritis (RA) has seen impressive improvements. New drugs with novel modes of action have led to improvements not only in signs and symptoms, but also in long-term outcomes, including joint destruction and disability. Therefore, the goal of RA treatment has changed from improving outcomes over the short term to outcomes over the long term. The proposal that there should be a paradigm shift from "care to cure" has become realistic.

The changes generated in the last 10 years have been carefully monitored since 2000 in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort [1, 2]. We previously reported that disease activity in the IORRA cohort improved significantly from 2000 to 2007 [3]; subsequently, there has been constant improvement along with the changes in the drugs employed for therapy (Fig. 1). Clinical remission has become a realistic goal. By any of the 2010 criteria for remission proposed by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR), the number of patients in remission has increased [4, 5] (Fig. 2). This progress has been the result of the increased use of methotrexate and biologics. Based on data mainly from IORRA, the maximum dose of methotrexate has been raised [6, 7], and this will lead to better patient outcomes over the next decade. It is amazing that changes in disease control have resulted from the use of nonsteroidal anti-inflammatory drugs as well as gastrointestinal medications (Fig. 3).

An IORRA study conducted in the prebiologic era found a standardized mortality ratio (SMR) of 1.46-1.90, which was consistent with findings from Western countries [8]. Advances in drug therapy may improve the survival of RA

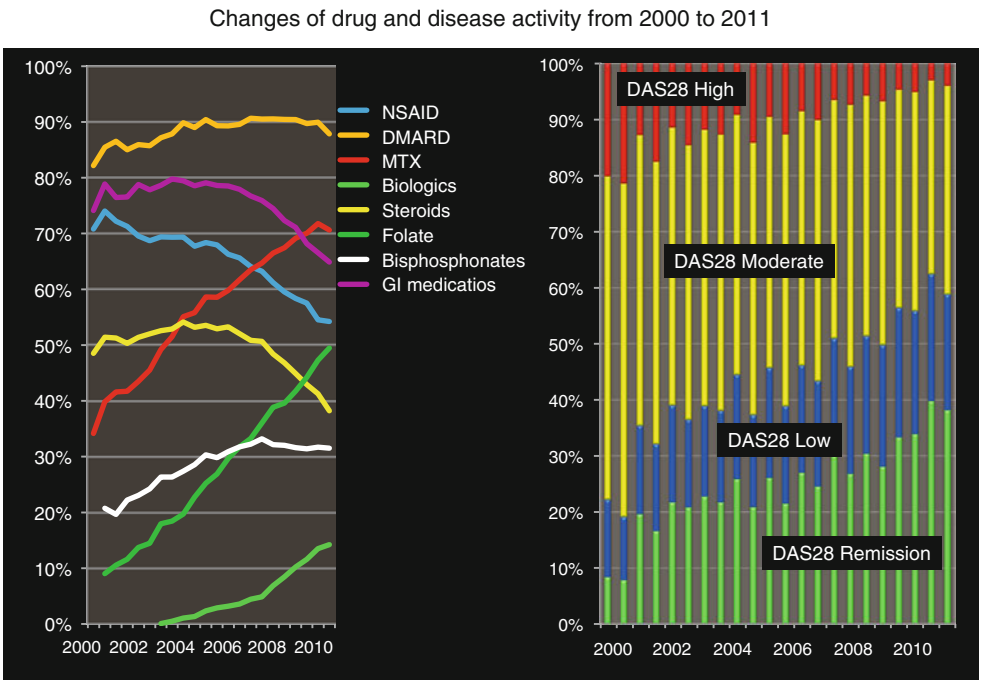

Fig. 1 Changes of drug and disease activity from 2000 to 2011. Changes of drug use and disease activity of RA patients in the IORRA cohort from 2000 to 2011 are shown. Disease activity was categorized by DAS28 according to the standard method

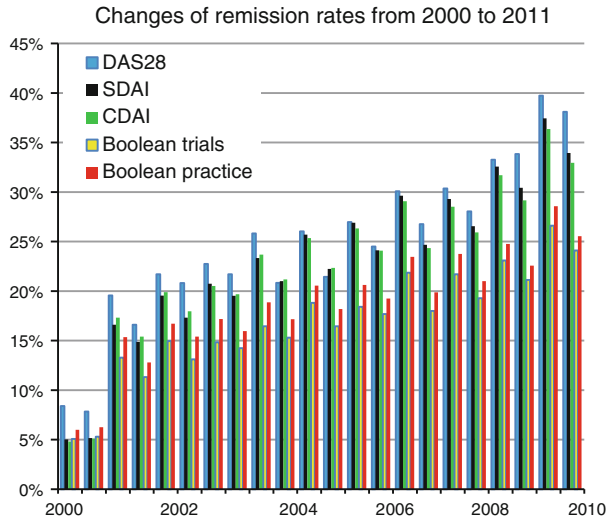

Fig. 2 Changes of remission rates from 2000 to 2011, defined by 5 methods including DAS28, simplified disease activity index (SDAI), clinical disease activity index (CDAI), Boolean trials, and Boolean practice. Definition of remission is based on each criterion

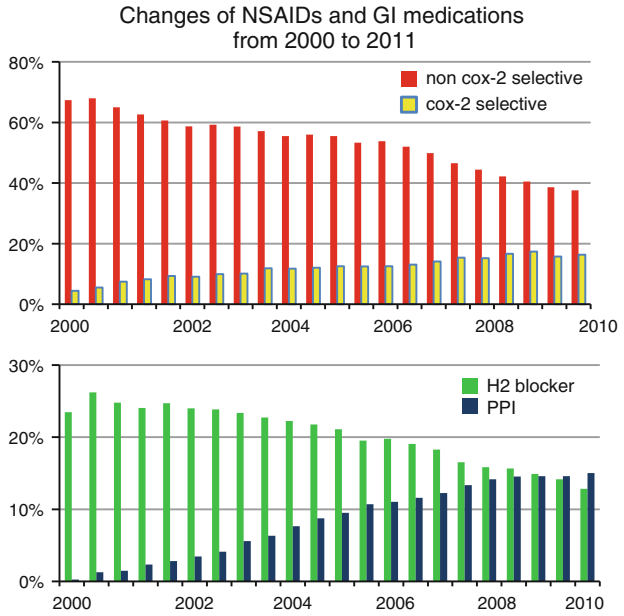

Fig. 3 Changes of use of NSAIDs (*upper column*) and gastrointestinal (GI) medications (*lower column*) from 2000 to 2011. NSAIDs were categorized by cyclooxygenase-2 (COX-2) selectivity as COX-2 selective (celecoxib, meloxicam, and etodolac) or non-COX-2 selective (others). Categorizations of proton pomp inhibitor (PPI) and H2 blocker are based on label information

patients [9]. We recently undertook a nationwide study to estimate the mortality rate of RA patients treated using biologics (Nakajima A, et al. submitted); our findings need confirmation by a more precise study. It is extremely important to recognize that the ultimate goal of the treatment of patients with RA is to improve long-term outcomes, including mortality and quality-adjusted life years (QALYs) [10].

We would like to emphasize that improvements in patient management have been achieved not only by new drugs. It is apparent that new drugs initiated these changes, but in addition, major improvements have been achieved in the overall approach toward treating patients with RA. The establishment of treatment recommendations [11, 12] for management of RA, and the introduction of new criteria for classification [13] and remission [4, 5], are important

platforms for introducing novel treatments into daily practice.

We previously reported several findings that support the concept that strict control of disease activity by maintaining the disease activity score using 28 joint count (DAS28) at a low value can inhibit the progression of disability in patients with RA [3, 14]. This target-driven therapeutic strategy ("treat to target") has become familiar as the T2T movement since recommendations for achieving optimal outcomes were published in 2010 [15]; we first reported on use of "treat to target" in 2007 [3].

Progress in the technology of imaging modalities, including ultrasound and magnetic resonance imaging (MRI), has led to increased accuracy of diagnosis. As suggested by the new classification criteria for polymyalgia rheumatica [16], the addition of ultrasound information will increase the sensitivity and specificity of the diagnosis of early rheumatoid arthritis. Although there remains the problem of feasibility, ultrasound should be widely implemented for routine care of RA patients [17]. These diagnostic strategies were established based on the results of several clinical studies, predominantly randomized controlled trials (RCTs) [18]. Comparing the study patients in RCTs with patients in daily practice is debatable, which we return to later in this review.

When we consider the changes that have occurred over the last 10 years, we can see that the strategies of RA treatment have changed dramatically as a result of the productive collaboration of academic expertise and innovative companies.

The future of the biologic era

Everyone can agree that molecular targeting is one of the best ways to control disease activity for a disease in which the target molecule has been identified. RA is phenotypically a quite heterogeneous disease, but the pathophysiology is quite uniform. Although many molecules are involved in the pathogenesis of RA, there are only a few key molecules that can be targeted for treatment. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been most successfully targeted, and the introduction of monoclonal antibodies and receptor-fusion proteins has successfully led to suppression of RA disease activity [19, 20].

There are several other candidate molecules that may be targeted for RA treatment, including CD86, CD20, CD22, and B cell activating factor (BAFF), which are functional surface molecules of T cells or B cells; and IL-17 and IL-12/23, which are proinflammatory cytokines [21, 22]. Antibodies and/or fusion proteins with activity against those molecules have been developed and are in clinical trials. In the near future, we may have more than 10 effective drugs for treatment of RA. The efficacy and safety profiles of these biologics may differ according to their target molecules, but an essential characteristic of these drugs is their ability to suppress joint destruction and improve long-term outcomes. Improvement in the signs and symptoms of each RA patient is a minimum requirement, but will not be sufficient for a candidate drug to become a useful therapeutic option.

It should be recognized that these macromolecular drugs cannot cross cell membranes, and are active extracellularly. Therefore, these biologics are quite safe with regard to hepatotoxicity, nephrotoxicity, and hematotoxicity. Concerns regarding the safety of biologics focus on the immunogenic reactions against exogenous proteins and the results of the suppression of target molecules. Preclinical and clinical data accumulated over the last 10 years have demonstrated that hypersensitivity to these macromolecules occurs at a tolerable level, and is manageable in daily practice. However, suppression of target molecules is a major problem affecting the safety profiles of these biologics; For example, TNF-α is part of the endogenous line of defense against tuberculosis infection, and suppression of TNF-α has resulted in increases in reactivation of occult tuberculosis infection [23]. Thus, it very important to predict the possible side-effects of any biologic by considering the role of its target molecule. However, all of the target molecules of the biologics used to treat RA are associated with the immune system of the host, and therefore susceptibility to infection is an unavoidable issue. Efforts have been made to identify patients highly susceptible to infection, so that an effective prophylactic regimen can be instituted; however, prevention of opportunistic infections, including pneumocystis pneumonia, remains an important concern [24].

Use of biologics to treat RA is a pharmacoeconomical issue. These macromolecules are quite expensive compared with other drug classes, because they are produced using advanced technology. The outpatient costs incurred from 2000 to 2007 for 8,982 RA patients (34,839 patient-years) enrolled in the IORRA study were evaluated. The mean annual outpatient cost increased from 287,626 JPY in 2000 to 366,964 JPY in 2007 (+27.6 %). The cost of medications and injections over those 7.5 years increased 39.0 and 1215 %, respectively. Costs increased in association with aging, increased DAS28 values, and increased Japanese Health Assessment Questionnaire (J-HAQ) scores. Levels of disability and use of biologics were the most significant factors associated with cost increases. Outpatient care costs for patients with RA also increased over the last 7.5-year period, especially after the introduction of biologics [25].

Extensive pharmacoeconomical analysis has demonstrated that biologics are cost-effective when work

productivity is taken into consideration, but cost is an obvious barrier to RA patients who have lost their job because of their disease. Our recent data have shown that biologics are most cost-effective when used in patients with early RA and with moderate disability (J-HAQ = 1.0–1.5) (Tanaka E, et al. submitted). In the effort to improve patient quality of life (QOL), this use of biologics for earlier disease is needed for effective utilization of limited medical resources.

Another promising approach for improving the cost benefits of biologics is the development of generic biologics, also known as biosimilar products [26]. Clinical studies of these biosimilar products are now being conducted in many countries, including Japan.

Antirheumatic drugs: DMARD to MTARD

Control of disease activity in RA had its origins in the empirical use of gold compounds in clinical practice, and was not the result of scientific evaluations. Gold compounds belong to the class of drugs called disease-modifying antirheumatic drugs (DMARDs). The target molecules of DMARDs, including gold compounds, D-penicillamine, sulfasalazine, bucillamine, and actarit, have not been clearly identified, but the targets of methotrexate, leflunomide, mizoribine, and tacrolimus have been well defined. Now there is a new class of drugs, including protein kinase inhibitors, which target unique molecules that regulate cell functions. Many of these drugs have been classified as immunosuppressive drugs. We propose a tentative generation-based classification of these immunosuppressive drugs according to when they were discovered (Table 1).

The molecular targets of the drugs in the 1st to 3rd generations were identified after discovery of the drug; however, the 4th generation of immunosuppressive drugs is a novel class of antirheumatic drugs that have been developed based on molecular targets. Thus, we would like to propose the designation "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs" (DMARDs).

Thus far, five oral compounds including kinase inhibitors (tofacitinib, fostamatinib, VX-509), an S1P lyase inhibitor (LX 3305), and a chemokine receptor-1 antagonist (CCX354-C) have been developed [27, 28]. Because there are many target molecules involved in regulating cell function in the immune system, many novel drugs classified as MTARDs should be discovered (Table 2).

MTARDs are small-molecule compounds with high specificity for the target molecule. In comparison with biologics, MTARDs are administered orally, and their production should be less expensive. Therefore, if they are noninferior to DMARDs, MTARDs would provide advantages over biologics, since biologics are not administered orally and are expensive.

Table 1 Immunosuppressants

Generation	Mode of action	Drugs
1st	DNA damaging agents	Cyclophosphamide, alkylating agents
2nd	Purine/pyrimidine antimetabolites	Methotrexate, leflunomide, mizoribine, azathioprine
3rd	Calcineurin inhibitors	Cyclosporine, tacrolimus
4th	Protein kinase inhibitors	Tofacitinib, fostamatinib

Table 2 Comparison of DMARDs and MTARDs

Class		Definition	Drugs
DMARDs	Disease-modifying antirheumatic drugs	Target molecule is unknown, or was identified after drug development	Gold, D-penicillamine, sulfasalazine, bucillamine, methotrexate, leflunomide, tacrolimus, etc.
MTARDs	Molecular-targeting antirheumatic drugs	Drug was developed directly to target the molecule	Tofacitinib, fostamatinib, etc.

The safety profile of MTARDs is a concern. MTARD actions occur intracellularly, and MTARDs must cross the cell membrane. Thus, cytotoxicity may be inevitable if MTARDs must be administered in high concentrations. In addition, regulation of intracellular protein kinases, the target molecules, is thought to be sensitive to concentration; therefore, changes in levels of protein kinases may lead to side-effects [29]. Since kinases are phosphotransferases, these kinase-inhibiting drugs will inhibit adenosine triphosphate (ATP) binding at the catalytic sites of kinases [30], and may nonspecifically inhibit ATP binding. In vivo and in vitro experiments should be performed for clarification. The results of phase 1–3 clinical trials of the first MTARD, tofacitinib, indicate that it was relatively well tolerated, and it has been submitted for approval in the USA, European Union, and Japan [31].

Importance of practice-based clinical studies

As mentioned earlier in this review, there are many guidelines and recommendations regarding therapeutic strategies for daily practice that have been established, including the most recent ACR recommendation [12]; however, it is important that these have been established based on the results of many clinical studies, including

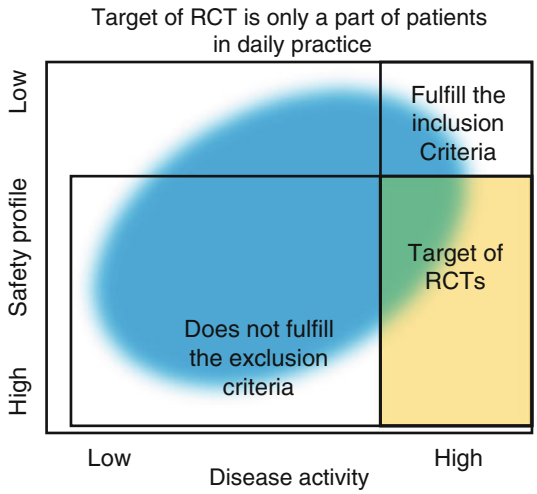

Fig. 4 The target of a RCT is only a part of the patients in daily practice. The target population of most randomized controlled trials (RCTs) is limited by the inclusion and exclusion criteria of the study. In most RCTs for RA, patient inclusion is dependent on disease activity and exclusion is dependent on safety profiles

many RCTs. RCTs are quite appropriate for determining the efficacy and safety profile of a drug or therapeutic strategy, but the population of study patients is usually restricted because of the study inclusion and exclusion criteria (Fig. 3).

It has been argued that only a small fraction of patients in daily practice would satisfy the inclusion and exclusion criteria of the clinical studies of biologics [17]; therefore, the therapeutic strategies established by clinical studies are acceptable but not ideal for implementation in daily practice. As Professor Furst has commented, "Well-designed clinical studies and observational cohorts, we need them both" [32]. Many RCTs have been conducted by pharmaceutical companies, but it is extremely difficult for a company to organize and maintain an observational cohort based on daily practice. There are many registries and observational cohorts of RA patients, including IORRA, CORRONA [33], NOR [34], and SRR [35]. We believe that consideration should be given to basing the guidelines and recommendations for RA therapeutic strategies on these practice-oriented databases. In addition, we would like to encourage clinical studies based on all the patients seen in daily practice (Fig. 4).

One of the pitfalls of evidence-based medicine (EBM) has been the application of the results of clinical studies that were conducted under medical conditions different from those of the patients in our daily practice. Even if the essential baseline characteristics are similar, the study patients might be of different ethnicities, with different comorbid diseases, concomitant medications, methotrexate doses, financial support, or medical insurance. These are the limitations of EBM, and we have to think about the application of evidence generated from "our" patients to patients in daily practice. We have established a large cohort of IORRA patients with RA, and various evidence-based findings can be generated by appropriate analyses; therefore, it is possible to apply the data from the IORRA cohort to our patients in IORRA. We call this approach "institute-based medicine" (IBM) or "IORRA-based medicine" (also IBM). It may not be feasible to apply this concept to all patients in all clinical situations, but we think that we have to try to improve the quality of evidence by considering the medical circumstances of each patient.

Thoughts on a patient-friendly program

The aim of RA treatment is the well-being of RA patients. Patient self-care is needed to prevent disease progression; however, RA is essentially not a lifestyle-related disease where patient effort yields a better outcome. Thus, medical professionals, including rheumatologists, must modify the course of the disease so that it leads to the best outcome. If patients are not educated about their disease, or are depressed by a poor disease outcome, effective treatment cannot be delivered. As treatment goals have become more optimistic over the years since the introduction of rigorous control of disease activity, there is also a tendency to administer stronger immunosuppression to patients. Both patients and health professionals have to be acutely aware of the early signs and symptoms of adverse events, including opportunistic infections, since anticytokine therapy may sometimes mask those signs [36].

Considering these issues, our IORRA cohort has been established essentially based on information from patients [1–3]. OMERACT has been conducting workshops on patients' perspectives for over 10 years [37], which has led to a recently published definition of RA remission from the patient perspective [38]. Thus, patient education and participation has become increasingly important. As a part of the T2T program, the patient version of the T2T program has been published [37] and translated into many languages, including Japanese. Furthermore, product-specific campaigns that focus on patients who are prescribed a specific drug have been developed, with an aim of specifying the important issues of care in daily life. These are welcome developments in the management of RA and may lead to better patient outcomes. Thus, rheumatologists must share their experience with their patients.

Future perspectives

It has been proposed that medicine of the future should be described by the 4 Ps: predictive, personalized, preventive,

and participatory [39]. Using this perspective, what we have to develop for management of rheumatoid arthritis is: better prediction of disease onset, progression, and response to treatment; a personalized therapeutic strategy; prevention of disease onset, worse outcomes, and side-effects; and participation of all rheumatologists and patients. In the future, use of genomic information [39–47] from individual patients should become important for predicting the disease and its course in each patient.

Furthermore, when thinking about the characteristics of medicine in 2020, we should include the developments of a postgenomic society, and of nanotechnology, smart IT, and enhanced performance [48]. It has been suggested that both medicine and healthcare should be incorporated into the big wave of technology investment.

In conclusion, management of RA has progressed remarkably over the last 10 years. However, there remains much for us rheumatologists to do for our patients.

Acknowledgments The IORRA cohort was conducted through the effort and collaboration of all staff at the Institute of Rheumatology, Tokyo Women's Medical University. IORRA has been supported by an unrestricted grant from Asahikasei Kuraray Medical Co., Ltd., Abbott Japan Co., Ltd., Asahikasei Pharma Corporation, Astellas Pharma Inc., AstraZeneca K.K., Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Daiichi Fine Chemical Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Dentsu, Sudler & Hennessey Inc., Eisai Co., Ltd., GlaxoSmithKline K.K., Hisamitsu Pharmaceutical Co., Inc., Janssen Pharmaceutical K.K., Japan Tobacco Inc., Kaken Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co. Ltd., Mitsubishi Chemical Medience Corporation, Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co., Ltd., MSD K.K., Mundipharma K.K., Nippon Chemiphar Co., Ltd., Nippon Shinyaku Co., Ltd., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sanofi-Aventis K.K., Santen Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sekisui Medical Co., Ltd., Taishotoyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, Teijin Pharma Limited, Torii Pharmaceutical Co., Ltd., UCB Japan Co. Ltd., and ZERIA Pharmaceutical Co., Ltd.

Conflict of interest H.Y. has been received speaking fee and/or consulting fee from Abbott, AstraZeneca, Bristol-Myers, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Janssen Pharmaceutical, Mitsubishi Tanabe, Otsuka Pharmaceutical, Pfizer Japan, Takeda Pharmaceutical, Teijin, and UCB. All other authors have declared no conflicts of interest.

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