Best Practice & Research Clinical Rheumatology 29 (2015) 543–549

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/locate/berh

2

Treating to target in established rheumatoid arthritis: Challenges and opportunities in an era of novel targeted therapies and biosimilars

Thasia G. Woodworth, MD (Visiting Clinical Research Scientist)[a,*], Alfons A. den Broeder[b]

[a] Division of Rheumatology, David Geffen School of Medicine, University of California (UCLA), Los Angeles, USA
[b] Dept. of Rheumatology, Sint Maartenskliniek, PO Box 9011, 6500 GM, Nijmegen, The Netherlands

ARTICLE INFO

Keywords:
Rheumatoid arthritis
Treat-to-target
Disease activity
Remission
Disease modifying antirheumatic drugs
Biologics and biosimilars

ABSTRACT

There is increasing consensus that periodic monitoring of disease activity status in rheumatoid arthritis (RA) patients to achieve and maintain remission, or at least low disease activity (LDA), the so-called treat to target (T2T) improves outcomes regardless of the duration of disease. Based on systematic literature reviews (SLRs) of clinical trials and registries, International Recommendations published in 2015 represent expert opinion describing efficacy and safety of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs). A total of 10 recommendations are detailed from four "Overarching Principles": (1) treatment decisions are shared between patient and rheumatologist; (2) the primary goalv is to maximize long-term quality of life by controlling the symptoms, preventing joint damage, and by normalizing the function and social and work participation; (3) abrogation (not just control) of inflammation is the most effective method to achieve this goal; (4) T2T by measuring disease activity regularly and adjusting therapy to achieve remission/LDA optimizes outcomes in RA.

The SLRs provide solid evidence that methotrexate is the "anchor" of csDMARD and that step-up therapy by adding/substituting other csDMARDs, such as sulfasalazine (SSZ), hydroxychloroquine (HCQ), or/and leflunomide (LEF) is as effective as combination therapy to initiate. Tofacitinib, a recently marketed csDMARD, may be more effective in comparison to MTX, and can be used in combination. Rapid disease

* Corresponding author. Tel.: +1 772 324 8844, +1 401 692 0103 (mobile).
E-mail address: thasia@woodworth.info (T.G. Woodworth).

http://dx.doi.org/10.1016/j.berh.2015.10.001

control can be achieved by "bridging" with various regimens of glucocorticoids (GCs), but tapering to doses $\leq$7.5 mg/day is critical to limit side effects. In practice settings, use of bDMARDs is influenced by reimbursement. Tumor necrosis factor inhibitors (TNFi) are highly used, but as more data emerge, there appear to be no major differences to more recently available targeted bDMARD monoclonal antibodies such as abatacept (co-stimulation blockade), rituximab (B cell depleting), tocilizumab (TCZ) (interleukin (IL)-6 receptor blockade). Rituximab appears to be most effective for seropositive patients, and tocilizumab may be more effective as a monotherapy in patients intolerant to csDMARDs.

Besides T2T, attention to managing treatment and optimizing outcomes should take into account potential adverse effects, such as risk of serious infection, as well as potential morbidity/mortality related to cardiovascular events, pulmonary disease, osteoporosis, diabetes, and fibromyalgia which often influence some measures, such as the Health Assessment Questionnaire (HAQ).

Introduction

Although there is no consensus on the definition of established RA (estRA), rheumatologists would likely agree that once an RA patient, especially one presenting with poor prognostic factors, has been treated with an initial T2T strategy and not achieved remission, that patient now suffers from estRA. Consistent with 2014 recommendations of an international task force [1], he/she requires monitoring and changes in treatment to achieve remission, or at least low disease activity, in order to limit/prevent joint damage and disability. In this chapter, we discuss the experience gained in applying recommendations [2,3] for achieving remission and low disease activity (LDA) with various treatment strategies. We also include updates regarding key clinical trials providing evidence for efficacy and safety, and, in some cases, cost-effectiveness, of available therapies, as well as novel agents in phase II/III clinical development, to try to address the persistent challenges of treating estRA. We also discuss risk mitigation strategies to limit the risk of serious infection, the most prominent safety issue during initial bDMARD therapy, but a persistent risk in treating estRA. The chapter that follows specifically addresses tapering/withdrawal of therapy for patients in sustained remission or low disease activity. Three other chapters discuss the longer-term consequences of persistent chronic inflammation, and in some cases the effects of treatment, in terms of bone quality/fracture risk and joint damage, as well as cardiovascular risk. Two additional chapters focus attention on ongoing research to enable quality of care, and to engage patients as partners in treatment decisions, as an opportunity to optimize adherence, self-management, and outcomes.

Implementing the 2014 International T2T recommendations in estRA

Compared with the recommendations from European League Against Rheumatism (EULAR) (2010, 2013) and the American College of Rheumatology (2012), the International Recommendations published in 2015 provide evidence in terms of the applicability, effectiveness, and safety for T2T (remission and LDA) in estRA patients. A systematic literature review (SLR) not only described five studies in early RA patients but also one study in estRA patients [4]. We also identified one estRA report in the abstract form (EULAR 2015 [5]). In the latter 2, one evaluates the addition of adalimumab under routine care (RC) compared with two T2T approaches, and the other examines T2T by the addition of conventional DMARDs with monitoring frequency according to initial disease activity. Table 1 summarizes the T2T studies in estRA patients. Interestingly, remission or LDA was achieved in $\sim$50% of patients in the Canadian study, with no significant differences between groups. In the other study, conducted in Columbia, South America and reported in a EULAR abstract, 44% of patients were