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Biologics in rheumatoid arthritis (RA) – recommendations for Swiss practice

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Summary

The new paradigm of therapy in rheumatoid arthritis is to aim toward early and complete remission, using a larger use of conventional DMARDs and biologic agents. The present recommendations were established through a consensus to help practitioners in their daily use of those agents, to reflect the current "best practice" in Switzerland.

Key words: *rheumatoid arthritis; biologics; anti-TNF; treatment optimisation; guidelines*

Scope and purpose

Many guidelines for treating rheumatoid arthritis patients are available, including US and European guidelines. This document, based on evidence and expert opinion, but without any formal and systematic process or review of the literature, presents what is regarded as current practice by the representatives of the Swiss university hospitals. Those recommendations are intended as a pragmatic help for Swiss practitioners to improve standard care in Switzerland.

Introduction

Rheumatoid arthritis (RA) is an immune mediated, chronic and progressive inflammatory joint disease [1] with autoimmune phenomena such as rheumatoid factor (RF) and antibodies against citrullinated cyclic peptides (anti-CCP-antibodies, ACPA), clinically characterised by the symmetric involvement of multiple small and large peripheral joints. RA is the most prevalent inflammatory joint disease in developed countries, affecting up to 1% of the entire population. RA may lead to bone erosions and cartilage destruction resulting in loss of joint function, severe handicap and work disability.

There are a few variables which help to predict aggressive disease course and guide therapy: Presence of RF, CCP auto-antibodies, high CRP/ESR, early bony erosions and extra-articular manifestations [2, 3]. Importantly, RA should never be regarded as trivial, and an early and adapted therapy has to be started as soon as possible. Every patient presenting with arthritis of more than one joint and lasting for more than 6 weeks should be evaluated by a rheumatologist for possible RA. The recent revision of the ACR/EULAR classification criteria presented at ACR 2009 acknowledges this need [4].

Treatment goals of RA therapy

There is currently no cure for RA, and the vast majority of patients will have to be treated for the rest of their lives and with well-defined objectives. With the broad variety of treatment options, the aim is early and complete remission, which means the absence of swollen and tender joints, morning stiffness and fatigue, as well as clinical and laboratory signs of systemic inflammation. Furthermore, the structural integrity of joints has to be monitored in order to prevent any (progression of) structural damage, and thus to prevent handicap and work disability.

The best validated tool for disease activity monitoring is the disease activity score (DAS). The DAS28 score includes the number of tender or swollen joints (out of 28 defined joints), acute phase reactants and a general health evaluation by the patient [5]. Despite limitations, this composite index is the international assessment tool used for clinical studies, and also to prospectively monitor disease with the aim to adjust treatment intensity [6–8]. The structural joint status is monitored by conventional X rays on a yearly basis. Joint ultrasonography is an ideal bed-side method to detect early structural changes, and this rapidly expanding technique will certainly become a standard. The Swiss Society for Rheumatology (SGR/SSR) provides a user-friendly web-based tool for longitudinal monitoring

and documentation of all necessary disease parameters (http://scqm.ch). This disease assessment should be completed on a regular basis, with annual radiographic analyses and patient-centred assessments of functional status and quality of life by standardised measures, such as the health assessment questionnaire of disability (HAQ-DI) or SF-36.

Early DMARD treatment

Patients with diagnosed RA should be started with a disease-modifying anti-rheumatic drug (DMARD) therapy as early as possible. Methotrexate (MTX) is the gold standard drug for mildly to highly active disease activity. The use of subcutaneous administration, starting with (at least) 10 mg per week and combined with folate substitution (5–10 mg per week) to minimise side effects is recommended. MTX dose should be increased by up to 25–30 mg per week within 2 to 3 months depending on efficacy and tolerability.

Monotherapy with other DMARDs such as anti-malarials, sulfasalazine and leflunomide is recommended for patients with low disease activity and a lack of bad prognostic markers. Combinations of MTX with other conventional DMARD have been tested in several clinical trials, and were shown to provide some increased efficacy without potentiating toxicity [9, 10]. Systemic or intra-articular glucocorticoids may be used to rapidly induce remission but the daily dose should not exceed 5 mg if given over prolonged periods (> a few weeks).

Indication for Biologics

Ongoing stringent monitoring of RA disease activity and progression, as recommended above, allows appropriate adaptation of DMARD and biologics treatment. The authors of this consensus agree that if low disease activity or remission (defined for practical purposes as at least a DAS28 $\leq$3.2) has not been achieved within 3 months with the initial conventional DMARD therapy, that the use of a biologic agent is recommended as the likelihood of reaching a low disease activity status, after initial failure of MTX, using subsequent conventional DMARDs is low [11].

At present, TNF blocking agents are the 1st choice for biologic treatment when conventional DMARD therapy has failed to induce disease remission. This recommendation is based on the good clinical experience with anti-TNF-therapy, their demonstrated strong efficacy, their rapid onset of action and the known benefit–risk profile with over a million patients treated up to date and more than a decade of experience with the use of the three TNF-blocking agents currently licensed for the Swiss market.

Prior to the initiation of any anti-TNFα therapy, a systematic workup has to be performed to exclude the various contra-indications to such treatment. The current recommendations in regard to this topic released by the Swiss Society of Rheumatology are available online (www.rheuma-net.ch/richtlinien).

The choice of the anti-TNF agent used is primarily based on the individual patient characteristics (such as compliance, preference for long dosing interval with intravenous administration or preference for self-subcutaneous administration, venous access) and the availability of the appropriate infrastructure for intravenous infusions. The authors believe there is currently no efficacy or safety data to suggest an overwhelming advantage of one agent over the others.

Whenever possible, it is strongly recommended to use any TNF-blocking agent in combination with MTX, as combination of both agents was superior to monotherapy with either one of these substances in all clinical trials, in terms of clinical response, physical function and radiographic progression [6, 12]. In the case of MTX intolerance, reduction of the MTX dose or use of an alternative DMARD such as leflunomide is recommended. Biologics, such as monotherapy, should only be considered when traditional DMARDs are contraindicated. Monotherapies were not shown to have superior efficacy compared to MTX, except tocilizumab, a humanised monoclonal antibody against the interleukin 6-receptor which was more effective in monotherapy than MTX alone. However, this study did not include a combination arm, and for the moment tocilizumab should also be used whenever possible in association with MTX [13].

Modification of biologic treatment

The disease course of patients on an anti-TNF therapy is not linear. Thus, disease activity has to be tightly monitored with treatment modification in case of a lack of/or insufficient efficacy, or a secondary loss of response, while some treatment de-escalations may be considered in the case of persisting remission.

Insufficient response or secondary loss of response:

If remission is not reached or is lost after an initial favourable response, modification or intensification of therapy is mandatory. In the setting of a significant clinical response, such as a good EULAR response, but in the absence of remission, treatment optimisation with a dose increase of the conventional DMARD and/or the addition of another DMARD, as well as short-term gluco-corticoids are reasonable options for the authors, even if no formal trials support these suggestions.

In the absence of a response, or if a tentative optimisation fails, the anti-TNF agent should be stopped and an alternative biologic agent should be used; either an alternative anti-TNF agent or a biologic agent with a different mode of action such as rituximab, abatacept or tocilizumab. Efficacy, in this difficult-to-treat TNF-resistant population, has been demonstrated for all of these agents in randomised controlled trials [14–16]. Whether changing to a second TNF blocker or to a biologic with a different mechanism of action is the better option has not been evaluated in head-to-head trials [17–24]. The preference for currently available treatment strategies in this setting still varies from centre to centre.

Remission

In case of remission, even if the optimal therapeutic strategy remains unknown, all centres agree that gluco-corticoids should be tapered first and discontinued whenever possible. The authors agree that the dosage of either the biologic or the conventional DMARD should not be modified for at least 6 months of persisting remission. Thereafter, treatment intervals of biologics are prolonged and

biologics are finally stopped with ongoing DMARD therapy.

Drug-free remission:

The ultimate goal of treatment would be an ongoing drug-free remission. Based on the results of the BEst study, it appears possible to discontinue anti-TNF therapy as well as concomitant DMARD in a small percentage of patients [25]. However, these patients were treated very early and very aggressively (combination of infliximab and MTX). The data led to the hypothesis that there exists a "window of opportunity" (i.e., an, as yet, undefined time slot in early RA) when it is possible to eradicate all disease processes and achieve a "re-set" of inflammatory and autoimmune phenomena. In such cases, it remains even more crucial to tightly monitor the patients for any signs of reactivation or structural damage progression, with prompt resumption of therapy if needed.

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