The ultimate treatment goal of RA is to control the inflammatory process, remission, without progression of joint damage, to maintain or restore normal physical function and capacity to work [1]. New developments have led to improved treatment outcomes, including early start of treatment, use of combination therapies, specific intervention with biological response modifiers and response-driven treatment [1]. We review the developments of treatment of RA, discuss current treatment strategies and whether to step up or step down treatment in patients with early RA.

Until the mid-1980s, treatment of RA was done by the pyramid approach, which involved the use of NSAIDs for years until joint damage developed and then giving DMARDs (Fig. 1) [2]. In this approach, most patients experienced poor long-term outcomes. As RA is a serious and chronic disease that requires early and intensive use of DMARDs, important therapeutic changes to RA have taken place in the past two decades. These changes relate to the increased number of more effective drugs being available, biological response modifiers, early treatment, the aim of remission and tight control of disease activity [1]. Thus, the traditional pyramid including the ‘go low, go slow’ approach has been replaced by a more early intensive treatment striving for remission.

Clearly, RA patients benefit from the early start of DMARDs and application of tight control. In daily practice, an early start includes MTX as the first choice of DMARD, because it is known to be clinically and radiologically effective causing relatively fewer toxic effects [1]. However, the question now arises as to which treatment strategy should be applied? Additionally, should MTX be initially combined with other DMARDs and should one of these DMARDs be tapered down in case of a clinical response, i.e. the step-down strategy? Or should MTX be given as initial monotherapy and in the case of suboptimal treatment response, a second DMARD added, i.e. the step-up strategy? Since both strategies have never been compared directly, it is difficult to prefer one over the other. However, we could suggest several considerations when choosing to step down or step up.

A window of opportunity may exist in which early treatment could allow the modification of early inflammation and prevention of development of joint damage; in other words the earlier, the better [1]. This approach should include a step-down strategy. For instance, intensive glucocorticoid therapy in combination with MTX and SSZ, applied as a step down [the Combinatie therapie Bij Rheumaatide Artritis (COBRA) scheme], has been shown to improve short-term clinical efficacy and may have long-term structural benefit in early RA compared with SASP monotherapy [3, 4]. However, we have concerns about whether the step-down approach should be the strategy of first choice.

First, the COBRA study showed only a small additional decrease in clinical efficacy after the withdrawal of glucocorticoids. Moreover, after 1 year, there was no difference in clinical efficacy between the COBRA scheme and SASP monotherapy [3]. In other words, the short-term efficacy was only temporary and mainly caused by the bridge therapy of glucocorticoids.

Secondly, despite comparable efficacies after 1 year, there was less radiographic progression in the COBRA group after 5 years of follow-up [4]. However, no data were available about sick leave and working capacity. Therefore, the question that still remains is: what is the clinical relevance of the detected difference in radiographic progression between combination and monotherapy? Thirdly, the existence of a window of opportunity in early RA is hypothetical and is, therefore, accompanied by uncertainties. On one hand, it is conceivable that hitting hard early in the disease and thus suppressing disease activity aggressively may result in a better long-term outcome. On the other hand, what is early disease or what is the timeframe of the window of opportunity: is there a beginning, is there an end?

Fourthly, a step-down strategy involves all RA patients being treated early and intensively. However, in ~30–40% of patients, sustained suppression of disease activity may be achieved with MTX monotherapy [5]. Therefore, we suppose that step down will lead to overtreatment.

In daily practice, the step-up strategy has been mostly applied with MTX as the first choice of DMARD and in cases of failure, a second choice of DMARD or addition of a biological response modifier. The tight control for rheumatoid arthritis (TICORA) study demonstrated that a step-up strategy comprising tight control in early RA led to significantly better clinical and functional outcomes compared with usual care [6]. Also, in daily practice, a tightly
controlled treatment using a step-up approach has led to high remission rates and low radiographic progression [7]. Compared with the step-down approach, by applying a step-up strategy the window of opportunity will be missed, which may result in less drug-free remission in the long term. Unfortunately, no such long-term data of step-down vs step-up strategies are yet available, although a few strategy studies have recently been published that compared initial combination therapy, like step-down with step-up combination therapy, including tight control in both strategies. Generally, the studies conclude that both strategies have comparable effectiveness. The Treatment of Early Aggressive RA (TEAR) study showed that initial triple (MTX, SASP and HCQ) therapy was completely comparable with a step-up triple strategy [8]. After 1 year, the number of patients achieving remission and the amount of radiological progression were similar in both groups. In the Guérir la PolyArthrite Débante (GUEPARD) trial, initial treatment with adalimumab combined with MTX was compared with initial treatment with MTX monotherapy and addition of adalimumab after 3 months in the case of 28-joint DAS >3.2. Although patients treated with initial combination therapy showed an earlier improvement in disease activity at 3 months, after 1 year the proportion of patients with low disease activity (65%) was similar in both groups and there were no differences in joint damage progression [9].

In a second TEAR study by Moreland et al. [10], no clinical differences were detected after 1 year between immediate combination therapy (MTX plus etanercept or triple therapy) vs a step-up strategy (starting with MTX and addition of etanercept or triple therapy in the case of no or low disease activity). Unfortunately, no data are yet given on radiographic progression [10].

On the basis of previous concerns about a step-down strategy (i.e. overtreatment and uncertainties about long-term effects in terms of work disability) and the latest results from strategy studies, we recommend the following treatment strategy in patients with early RA: a step-up treatment strategy starting with MTX monotherapy, including initial corticosteroids to bridge until optimal efficacy of MTX is achieved, followed by the rapid addition of biological response modifiers in case of an insufficient response. Additionally, patients should be treated as early as possible after diagnosis of (likely) RA and followed intensively for the effect of therapy (tight control). In the case of remission not being achieved, treatment must be changed until ultimately a state of sustained drug-free remission is reached. Last but not the least, many different ways of prescribing DMARDs/biological response modifiers are available but definite conclusions about the perfect strategy can still not be drawn. Therefore, we encourage more (cohort) data collection from daily practice to enable documentation of efficacy from different treatment strategies specifically and long-term outcomes of RA generally.

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