DMARD use in early rheumatoid arthritis. Lessons from observations in patients with established disease

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ABSTRACT

The concept of early and aggressive therapy of rheumatoid arthritis (RA) has been well documented in the past years. It includes immediate DMARD institution after diagnosis, the use of the most effective DMARDs, and rapid switching of regimens if a level of disease activity close to remission is not achieved. In this review we briefly explore to what degree this new concept has been implemented in routine clinical care. Based on an observational dataset comprising 3342 DMARD courses, we present evidence of a change in DMARD patterns in newly diagnosed RA patients towards a higher prescription rate of more aggressive drugs like methotrexate (MTX), as well as a decreasing lag time until MTX was instituted in RA patients over the years. One consequence of recent changes in therapeutic strategies is that comparative analyses of formerly versus recently employed DMARDs will be considerably biased in observational studies. By contrast to changes in DMARD usage, survey data show neither a shortening of referral time nor a change in the approach to diagnose early RA. These data indicate a need for more dissemination of the early arthritis concept.

Growth of a new concept

The therapy of rheumatoid arthritis (RA) is based primarily on disease modifying antirheumatic drugs (DMARDs). Over the past few years several new DMARDs, including biological agents, were approved and have expanded the armamentarium of therapeutics for RA. Nevertheless, even with these drugs,in clinical trials the majority of patients with established disease do not achieve 50% improvement by ACR response criteria (1-5), let alone cure. However, not only have the regimens changed during these years; the strategy of treatment has also changed (6), with the aim now being remission. Moreover, it has been postulated that the biological process changes very early in the disease course and that therapeutic interventions within a small window of time can reset the process of disease progression (7, 8). This "window of opportunity" reflects the rheumatologists'hope for long-term remission and cure.

The evidence to support such an approach initially came from therapeutic data in established, but still early RA (9), and was indirectly confirmed by meta-analyses (10), trial extension studies (11), and observational studies (12). Most clinical trials in early RA have been designed to compare the efficacy of different DMARD regimens (13-18), or DMARDs versus placebo (19). Some of these studies included combination therapy arms (13-15, 17, 20), which suggested that on a group level *a priori* combinations of DMARDs were not more effective than the individual DMARD components, unless glucocorticoids were employed in the combination therapy but not in the comparator arms. Only a few studies exist which evaluated different time-related strategies, such as very early versus delayed treatment introduction, and these speak clearly for the benefit of very early DMARD therapy (7, 8, 21). Nevertheless, no conclusive data are currently available in which patients with presumed increased risk of persistent, erosive disease have been followed on different therapeutic regimens (20, 22). Aside from the importance of obtaining the respective clinical results, such trials could also validate the different algorithms.

Another important development in the last decade is the recognition of the particular efficacy of two long-established DMARDs, methotrexate and sulphasalazine, especially when used at

high doses (23-26).

Thus, the concept that has emerged over the past 5-10 years includes: (i) institution of DMARD therapy immediately at the time of diagnosis; (ii) use of the most efficacious and most rapidly effective DMARDs with rapid escalation to appropriately high doses; and (iii) rapid changes in DMARD strategy if improvement does not reach a remission-like state of disease or at least comes close to it.

Implementation of the new concept

1. Change in the pattern of initial DMARDs

Looking at our own observational data which covers 3342 DMARD courses going back to the 1980s, the median lag time until DMARD initialization has been 12 months from the onset of symptoms (percentiles: 5 mo; 44 mo) in newly diagnosed patients. These numbers are derived from the clinics of two major hospitals in the Vienna area where patients are seen who are either self-referred or referred by their general practitioners or internists. This lag time is due mostly to delayed patient referral and still seems reasonably short, considering the pyramid approach that was still being employed in the early 1990s. An analysis of the potential differences between consecutive DMARD courses confirmed the importance of early therapy (27): regardless of the lag period until DMARD initialization, patients receiving first DMARD courses achieved significantly longer retention rates and a greater reduction in the acute phase response, a surrogate marker for short- and long-term improvement (28-30), than patients on subsequent DMARD courses (Fig. 1).

Importantly, when we look at the type of DMARDs employed in DMARD naïve patients, we realize that there has been a major change in the utilization of these drugs, particularly in the last decade. Figure 2 shows the proportional application rates over time for four typical DMARDs. As previously reported (27), the use of antimalarials (AM) has decreased considerably. In the early 1990s, up to 50% of the first DMARDs prescribed for new RA patients were antimalarials (AM), but this proportion has decreased to only about 20% more recently. On the other hand, only a few newly diagnosed RA patients received methotrexate (MTX) as their initial therapy in 1990, whereas since 2000 more than 50% of patients have been treated initially with MTX. Therefore, a major change in the patterns of initial DMARD choice has already taken place. These observation-

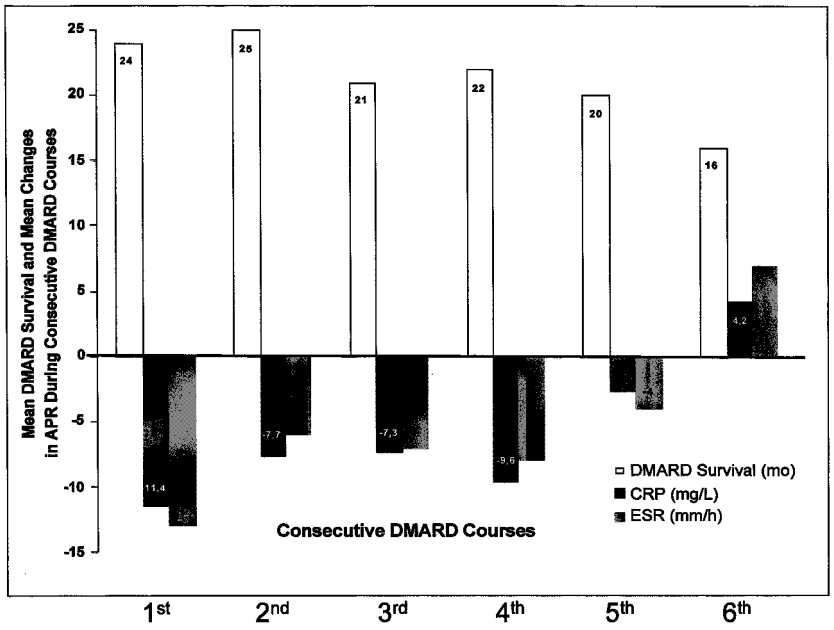

Fig. 1. DMARD survival and changes in the acute phase response (APR) during DMARD treatment. Survival of DMARD treatment (white bars,in months):all patients who received their first DMARD at our hospitals were included (n = 1,213). Survival distributions for the consecutive DMARD courses differed significantly (Breslow test statistics): p = 0.005.
Changes in acute phase response (CRP: dark grey bars, in mg/L; ESR: light grey bars, in mm/h): all patients with first DMARD administered at our hospitals plus baseline values of ESR > 10 mm/h (n = 861) or > 1 mg/L CRP (n = 577) were included; relationship between the DMARD course and APR changes is linear (test for linearity based on one-way ANOVA): p < 0.001 (ESR) and p = 0.005 (CRP).

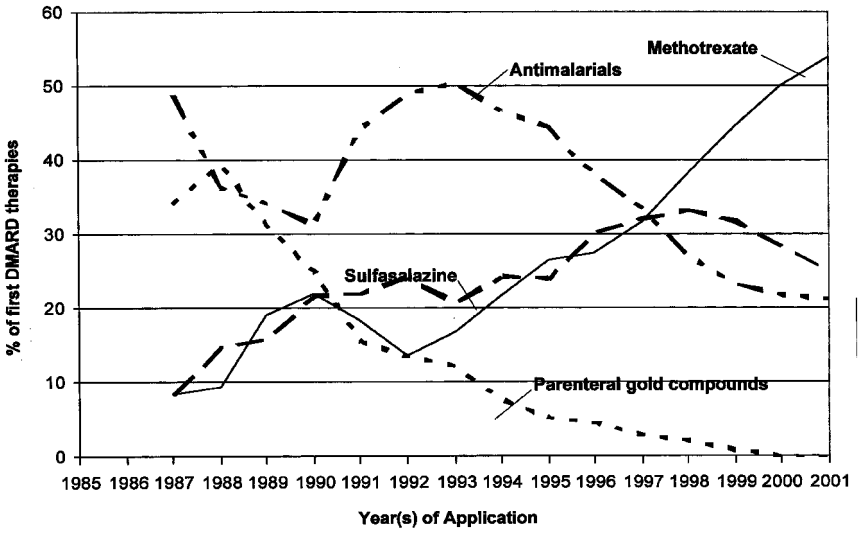

Fig. 2. Initial DMARDs for patients with RA during the period 1985-2000. Frequency of DMARD starts (gold compounds,antimalarials,sulfasalazine, and methotrexate) in DMARD naïve patients with recent onset RA (disease duration ≤ 18 months) over time (n = 1,213; other types of initial DMARDs included). The proportion of prescriptions is expressed by the means of 3-year moving averages to smooth the curves (e.g. 1987 = mean of 1985-1987).

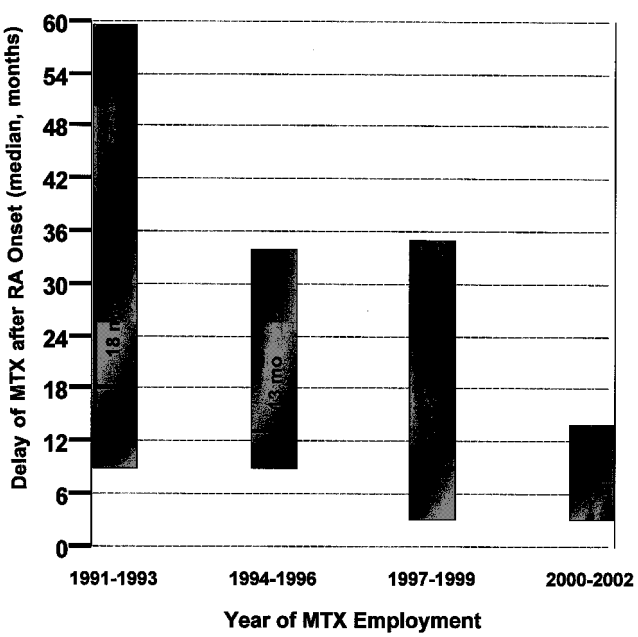

Fig. 3. Time to first use of methotrexate (MTX) in patients with rheumatoid arthritis (RA) over the years. All RA patients who had received their first DMARD at one of the study hospitals were included (see Fig. 2). The timing (3-year groups) of their first MTX prescription was noted and plotted against the time from the onset of symptoms. (Black line: median; boxes: interquartile range). Of the 1,213 initially DMARD naïve patients,725 (59.8%) had been prescribed MTX by the date of the analysis. The decrease in lag time was significant using the Kruskal-Wallis test ($p < 0.001$).

al findings are in line with the results of a survey of rheumatologists from various countries, in which an increase in the prescription rate of both MTX and SSZ was observed even between 1997 to 2000 (31).

2. Earlier treatment with methotrexate

Another type of analysis of early therapy which can be assessed by long-term observational data from patients with established RA is the question of how long it takes until methotrexate, the current gold standard in RA therapy, is employed after the onset of symptoms. Figure 3 shows the change in this lag time over the past decade (1991-2002) in 3-year intervals. In line with the data on the change in DMARD patterns described above, this lag time decreased considerably from a median of 18 months in the period 1991-1993 to 7 months in 2000-2002 ($p < 0.001$ in the Kruskal-Wallis test). For these analyses we included all patients who had their first DMARD prescription documented at one of our centers. The lag time overlaps with the time elapsed from first symptoms, obtained by history taking, until presentation at one of the clinics. Moreover, the new drugs, such as leflunomide and the TNF-antagonists, were not employed in MTX-naïve patients at the study hospitals.

3. Implementation from an international view

To foster the approach to very early therapy of RA, early referral constitutes the most important prerequisite. However, as we examined the practical realization of this concept by analysing questionnaires sent to practicing rheumatologists, we found that between the mid-1990s and the year 2000 there was no shortening in referral time of early arthritis patients to rheumatologists (31). This further characterizes a significant problem, that of the implementation of early referral in daily practice. From a practical point of view, this is the most important step, based on new research evidence. The goal of early treatment requires further efforts in the general medical community. To further assess these developments, a 2003 update of questionnaire-derived data is in progress, and will provide insights into the most current level of realization of the diagnosis and treatment of early RA. Importantly, about 50% of practicing rheumatologists initiate DMARD therapy only upon fulfilment of the ACR classification criteria (31). Since ACR criteria are often not fulfilled in early RA (32), this finding calls for the search and widespread validation of novel diagnostic and likewise prognostic criteria (33, 34)

Consequences for future studies

"Failure" of DMARDs, mostly due to adverse events or insufficient efficacy, is a common strategic problem in the treatment of RA. This is emphasized further by the evidence discussed above that the need to switch DMARDs early is indicative for a reduced likelihood of long-term treatment effects for the subsequent therapies (10, 27).

Given the relative inefficacy of traditional DMARDs (particularly if employed at insufficient doses) and the prevailing fear of their toxicity, rheumatologists previously aimed at maintaining patients on a particular DMARD if some improvement (and no major toxicity) had occurred. This past approach, which tended to be consistent over time, allowed for a relatively good estimate of DMARD effectiveness in observational studies by employing life-table analyses of drug retentions (23, 35, 36). However, the current aim for remission is changing the timing of new DMARD prescription, namely towards faster "on-off rates" of different types of DMARDs, particularly in patients who are only partial responders and not near complete remission. The availability of effective new agents, such as leflunomide and TNF-antagonists, which are used with increasing frequency and increasingly earlier in the disease course, has further enhanced this behavioural change, such that DMARD retention rates (aside from toxicity) will reflect remission and near remission rather than low grade effectiveness.

The pattern of DMARD use may further change after data from trials investigating a combination of TNF-blockers with MTX in comparison to single agent therapy, currently under way, will become available later this year. In consequence, observational studies on the

effectiveness of new DMARDs, and particularly comparative retention analyses of new versus traditional DMARDs, will tend more and more to reflect these trends in clinical practice. However, if long term continuation of the new therapeutic strategies will be the rule, observational analyses will now allow the rheumatology community to obtain more insights into the true capacity to effect remission of individual agents.

Conclusion

The value and long-term benefit of DMARD treatment in early rheumatoid arthritis has been well documented in the past years. Current research is focussed on early diagnosis and the prognostic implications of early therapy. Data showing a true slowing of what was called "the natural history of the disease" gives hope for millions of patients with RA. However, at this time the potential impact of these findings has not yet been translated into standard clinical care. Apart from clinical trials on early treatment, lag times in patient referral and delays in therapy remain a problem. It required about 15 years before the current gold standard of therapy, namely methotrexate, made its way to become the most commonly employed DMARD in newly diagnosed and early arthritis patients. It would be desirable that the process of treatment reinforcement without delay in early RA could be implemented in clinical practice more quickly.

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