RHEUMATOLOGY

Editorial

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The use of glucocorticoids in early rheumatoid arthritis

GCs versus other treatments and patient perceptions

While glucocorticoids (GCs) are still widely used in the treatment of RA, the debate between believers in their central role within the early RA treatment paradigm and advocates of the earlier introduction of biologics is ongoing. This editorial focuses on recent literature on this topic and critically reviews the important issues in this field, not least the perception of patients.

Major progress has been made in managing RA, with the applications of early intensive therapy and treat-to-target (T2T) principles. The Behandel Strategieën (BeSt) trial demonstrated a faster clinical improvement on initial step-down combination therapy with classical synthetic DMARDs (csDMARD) and GCs or MTX and a biologic, compared with csDMARD monotherapy. However, a continued T2T approach resulted in comparable long-term outcomes, making drug-free remission, prevention of functional deterioration and clinically relevant radiographic damage, and even normalized survival an achievable goal in several patients over all randomization groups [1]. Not unimportantly, there were fewer dropouts in the early infliximab arm compared with other treatment arms, including the early GC arm, at least partly as a consequence of perceptions on the therapeutics used [2]. This urges the rheumatological community to critically reflect on cost issues related to biologics but also on opportunities for a more effective use of low-cost drugs and the need to correct negative preconceptions about drugs like MTX and GCs. Using the friction cost method, the BeSt authors reported that costs to achieve a better quality of life are too high using infliximab with MTX for initial remission induction and that a combination with GCs should be preferred. They suggested that infliximab costs could be compensated for by productivity savings, but admitted their 2 year cost–utility analysis did not prove this [3].

Evaluating the reasons for dropout in clinical trials is important to determine the effectiveness of therapeutic strategies in view of their implementation in practice. Differences in drug combinations and dosages could influence effectiveness of initial treatment schedules, for instance by affecting the speed of response and the reporting of side effects, but patient perceptions might also contribute to this. This inspired researchers to evaluate monotherapy instead of combination therapy with csDMARDs and/or lower GC dosages in early RA [4, 5]. In the Combinatietherapie Bij Reumatoïde Artritis (COBRA)-light trial many patients ultimately ended up on biologics, probably due to too stringent targeting of remission, while only 40% were able to taper GCs to zero at year 1 [5]. In the treatment in the Rotterdam Early Arthritis Cohort (tREACH) trial, a large proportion of participants stepped up to biologics following very stringent T2T rules and the proportion still on GCs at year 2 was not mentioned [4]. Interestingly, a 2 year prednisone treatment of 10 mg daily on top of tailored weekly MTX in Computer Assisted Management in Early Rheumatoid Arthritis trial-II (CAMERA-II) was very effective and reduced the need for biologics [6]. Recently the Care in early RA (CareRA) trial [7] showed up to 60% DAS28-CRP remission at year 1 with the COBRA-slim regimen (MTX monotherapy and prednisone bridging: 30 mg starting dose tapered to 5 mg at week 5 and stopped after week 28), while treating to a target of DAS28-CRP low-disease-activity. There was no benefit of an early combination of csDMARDs (in contrast to the tREACH trial) or the initiation of a higher GC dose (60 mg prednisone). On the contrary, less discomfort was reported with COBRA-slim leading to even better effectiveness. Although not specifically powered for this, the CareRA trial showed that patients with so-called good prognosis benefited from COBRA-slim compared with MTX step-up without GCs. A general effectiveness analysis over all of the study arms showed very limited use of GCs at year 1 (5.2%) and only 7.5% had to start a biologic (2/98 patients on Cobra-slim in the poor prognosis group). Partly based on these results, the new 2016 EULAR recommendations for RA treatment call for starting csDMARD monotherapy—preferably MTX—and a short course of GCs [8].

Based on evidence from the trials above, different factors seem to determine treatment effectiveness: firstly, monotherapy with csDMARDs and a lower initial dose of GCs is associated with less discomfort and a higher retention rate compared with the original COBRA regimen. Secondly, treating to a target of low disease activity instead of remission is associated with a more effective use of csDMARDs, leading to decreased need for biologics and even better remission rates at year 1. Thirdly, it is feasible to reach high remission rates and stop GCs completely in the vast majority of patients after induction with GC-based schedules like COBRA-slim, and lastly, so-called good-prognosis patients (RF and anti-CCP negative, no erosions) benefit equally well from GC-based treatment as poor-prognosis patients.

When trying to implement the above treatment principles, one should not forget the poor compliance of practitioners

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with general recommendations. Understanding the hurdles and opportunities, for patients, rheumatologists or other health professionals, is essential. However, differences in health care systems might also affect the successful implementation of recommendations. There is no doubt that patients want to get back to normality as soon as possible [9] and the reasons given by rheumatologists not to implement early intensive therapies, including the temporary use of GCs, are not always in line with patient perceptions [10]. Patients are willing to take GCs if they have trust in their physician and are educated about the preventive measures needed to avoid side effects, and most importantly when they notice a rapid and persistent disease control. The ability to stop GCs might even give a strong sense of personal control. Although specific aspects might need attention in different countries, strategies like COBRA-slim are attractive in many parts of the world where the (early) use of biologics is not realistic for economic reasons. Despite adequate integrated care, optimal patient education and correct shared decision making, in some patients the above strategies will fail to control the disease and biologics or other targeted therapies such as the new 'inibs' will be needed. Pragmatic, smartly designed trials, including cost–utility analyses and data on patient participation, will be required to further determine the place of biologics in the early RA treatment paradigm.

To summarize, a favourable outcome of RA is achievable with an early T2T approach, starting with cheap drugs like MTX in monotherapy, appropriately dosed and temporarily associated with GCs. Conditions are a better understanding of patient perceptions and correct patient education to optimise shared decision making. This requires an important effort from rheumatologists and other health professionals and deserves a correct financial compensation, an investment that will pay off in improved outcomes—something that is particularly important for patients—and this hopefully will benefit most patients in all parts of the world.

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