



## Editorial

### Triple therapy in rheumatoid arthritis<sup>☆</sup>



### Triple terapia en la artritis reumatoide

Lydia Abásolo Alcázar

Unidad de Gestión Clínica (UGC) de Reumatología, Instituto de Investigación Sanitaria, Hospital Clínico San Carlos (IdISSC), Hospital Clínico San Carlos, Madrid, Spain

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovitis and systemic inflammation. Its prevalence varies little between countries, being 0.5% in our country.<sup>1</sup> The disease is associated with severe morbidity, impaired functional capacity and disability, decreased quality of life, loss of independence and increased mortality.<sup>2</sup>

In the last 20 years, the management of patients with RA has changed dramatically and RA therapies now focus on remission or at least a reduction in the inflammatory activity in order to reduce or prevent joint damage and disability. This has been prompted by several reasons: early therapy, dose optimization, use of combination therapies and the emergence of new forms of treatment. According to the study of Welsing et al.,<sup>3</sup> the disease has a better prognosis in recent decades, and this may reflect earlier diagnosis and a proper treatment more than a change in the disease characteristics.

All these advances in the management of RA have provided rheumatologists today with a wide therapeutic arsenal and many published recommendations and guidelines that aim to aid the physician in making decisions. Within these recommendations, perhaps the use of triple therapy in combination therapy is less characterized and its use is less widespread. The guidelines of the American College of Rheumatology (ACR) 2012<sup>4</sup> and the Canadian Rheumatology Association<sup>5</sup> 2012 recommend the use of combination therapy with disease modifying antirheumatic drugs (DMARDs), including triple therapy in patients with early RA, with moderate or severe disease activity and poor prognostic factors associated. Combination therapy should also be considered in patients who have an inadequate response to monotherapy.

The EULAR 2013<sup>6</sup> recommendations are less explicit in the use of combined therapy and triple therapy. They report that in patients that have not received prior DMARD, that the use of monotherapy or combination therapy is justified. If the goal of treatment is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, the clinician should consider switching to another DMARD strategy.

In the 1990s the first studies in the literature showing the benefit of triple therapy versus monotherapy, particularly methotrexate, sulfasalazine and hydroxychloroquine (HCQ+MTX+SLZ) appeared. In the study by Möttönen et al.,<sup>7</sup> the efficacy and tolerability of the combination of MTX+SLZ+HCQ and low-dose prednisone was compared to monotherapy, with or without oral prednisone in RA patients with early and active disease. Combination therapy was significantly better and was no more dangerous than monotherapy in remission induction. O.Dell<sup>8,9</sup> shows that, in patients with established RA, combination therapy with MTX+SLZ+HCQ was more effective than MTX alone or MTX+SLZ, with no differences in the percentage of adverse events. Katchamart et al. published<sup>10</sup> in 2009, a systematic review with a meta-analysis of the efficacy and toxicity of MTX monotherapy versus MTX combined with traditional DMARDs. With regard to triple therapy, they conclude that the combination of MTX, SSZ, and HCQ shows improved effectiveness/toxicity than MTX alone (hazard ratio 0.3, 95% CI 0.14–0.65).

Recently, a study by de Jong et al.,<sup>11</sup> also evaluated the effect of corticosteroids in different treatment groups. It compared, in patients with early RA, the clinical efficacy of triple therapy with classic DMARDs (MTX+SLZ+HCQ) and a regimen (oral or intramuscular) of corticosteroids compared to treatment with MTX monotherapy and an oral steroid regimen. Clinical improvement with fewer escalations is quickly reached and maintained with triple therapy so. No significant differences in radiographic progression serious adverse events were found. In any case, the proportion of patients with medication adjustments due to adverse events was

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E-mail address: [lydia.abasolo.hcsc@salud.madrid.org](mailto:lydia.abasolo.hcsc@salud.madrid.org)

significantly higher in those taking triple therapy versus monotherapy.

Since the year 2012 there have been several published studies of triple therapy combinations where biological agents were included. Van Vollenhoven et al.,<sup>12</sup> published a clinical trial that compared the addition of an anti-TNF (infliximab+MTX) agent to MTX with the addition of sulfasalazine plus hydroxychloroquine in patients with early RA who had not responded to MTX (MTX+SLZ+HCQ). The proportion of patients with good clinical response at 18 and 24 months of treatment was similar in both treatment groups. At 24 months, radiographic disease progression was significantly higher in patients receiving triple therapy than in those receiving biological treatment (mean 7.23 versus 4,  $P=0.009$ ). However, improved radiographic results after 24 months must be weighed against the lack of a convincing clinical difference at 24 months with substantially higher costs in the group with biological drugs. Similar clinical outcomes were seen by O'Dell et al.,<sup>13</sup> in 2013 for patients with established and active RA despite treatment with MTX, showing that the clinical benefit was similar in the triple therapy group (MTX+SLZ+HCQ) to that seen in the etanercept plus MTX group. Moreland et al.,<sup>14</sup> in 2013 compared in early RA, and with disease activity, the following strategies. Etanercept+MTX versus immediate triple therapy (MTX+SLZ+HCQ) or triple step therapy. After 102 weeks, all 3 strategies were more effective than MTX monotherapy before starting step-up therapy, but slower in reaching clinical objectives than the initial combinations. With regard to radiological progression, the group assigned to receive MTX+etanercept had a smaller increase in radiological Sharp scores compared with those receiving triple therapy (0.64 vs 1.69=0.047). There were no differences across treatment groups in the number of serious adverse events. Under the "real life" conditions, decision making in patients with RA is certainly more complex than in clinical trials. No selection of patients exists and treatment must be performed in an outpatient basis in an environment of rising health care demands and limited time available. Furthermore, in clinical practice, there are many factors that influence the choice of treatment for a specific patient with RA. This is the result of a decision process which usually influences the activity of the disease itself and certain physician and patient characteristics. Thus, the current tendencies in light of new knowledge on the management of RA, prior treatment and the reason for its suspension, consideration of comorbidities, age, disability and patients' concomitant medications, or patient preferences and treatment adherence, and certain economic factors, are influencing the decision process of the rheumatologist. This leads the rheumatologist, in many cases, to use combinations of treatment regimens, that although have efficacy and safety profiles that are not analyzed in the scientific literature, are based on clinical experience in order to shuffle the different options available. For example data from our hospital shows that, in 2012, 35% of patients were taking combination therapy and 5% had triple therapy. The most used combinations were MTX+SLZ+HCQ, MTX+leflunomide+biological agent, MTX+HCQ+biological agent and leflunomide+MTX+HCQ. The follow-up visits of patients with RA, which occupied about 50% of all subsequent visits, aimed to maximize the number of remissions of the disease, and to minimize the impact of adverse events, which are a major cause of treatment failure and morbidity. We should not forget this aspect and, in this sense, it is important to note that although the level of evidence is low, in contrast to the main benefits of combination treatments in general, it seems that combination therapy may result in more suspensions<sup>15-17</sup> than monotherapy due to toxicity. Many questions remain on the risks of different combinations strategies through a range of adverse effects, from the relatively minor to serious and potentially deadly problems. In summary, we can say that triple therapy is an appropriate option

for the management of our patients. Specifically, the combination of MTX+SLZ+HCQ has been shown to be more effective than monotherapy and some combination therapies in treating RA. It also appears that the combination of MTX+SLZ+HCQ is not inferior to some MTX combination therapies with biological agents, although it appears from recent studies that there is less radiographic progression with biologicals, but no clinical consequences. Based on current scientific data, triple therapy and combination therapy with DMARDs, in our view, should be more explicitly included in any clinical treatment guideline of RA. In our view, it is necessary to develop observational studies based on clinical practice, to adequately assess the efficacy and safety of different regimens of treatment combinations used by rheumatologists.

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