Steroid sparing therapeutic approaches to polymyalgia rheumatica-giant cell arteritis. State of the art and perspectives

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ABSTRACT

The therapeutic approach to polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) remains mainly based on corticosteroids. A few studies in PMR suggest a steroid-sparing effect with methotrexate in a subset of patients. No real alternative to steroids exists in GCA. Given the high chance of long-term treatment with corticosteroids in both diseases, randomized controlled trials with new immunosuppressive steroid-sparing drugs are eagerly awaited.

Between the two opposite sides of the Atlantic ocean, a dispute lasting several years about whether steroid therapy in polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) could be stopped before a two-year period or not, was kept on (1, 2). This is not a trivial problem because it underlines two crucial issues: (1) whether PMR in particular might really be considered a benign disease as initially hypothesized by Cecil and Kammerer in 1951, and as recently re-proposed by Salvarani and co-workers; (2) or whether alternatively PMR must be considered a forme fruste of vasculitis, similar in many respect to GCA, as hypothesized by Weyand *et al.* in 1994.

The obvious consequence of these different views is that a long-term therapeutic approach with corticosteroids leads to severe co-morbidities. Recently the Mayo Clinic study has substantially confirmed the European view. Both PMR and GCA patients needed in fact a median duration of treatment of 1.8 years, the range being between 0.08 and 19.4 years (3). Most importantly the median cumulative dose of prednisone during the treatment period, was between 4.5 and 5.4 g (range 0.2 - 42.5 g), and with such doses several important side effects were shown. The patients had a 2-5 times greater risk compared to age-matched controls, of developing diabetes, and vertebral, femoral neck and hip fractures.

All of these data clearly suggest that we need to improve our therapeutic program for PMR as well as GCA, and we must say that the available studies on alternative pharmacologic agents are scanty and not conclusive.

When facing the possibility of an alternative program, we must first focus on the best possible target. The first question therefore is : Do we have a clear target in PMR ? Do we have a clear target in GCA ?

Immunophenotypic and functional studies performed on peripheral blood cells as well as on mononuclear cells obtained from temporal arteries have disclosed that GCA certainly is a T cell-dependent disease. The cytokines expressed and synthesized are those of a TH1-dependent process, and of an activated macrophage-embedded milieu. In PMR we have clear evidence of an activated monocyte-related disease in the peripheral blood and in the tissue, with less evidence of a T-cell dependent inflammation.

If this is the panorama of the biology of the two diseases, then molecules acting on these events should be the main focus of our therapeutic interest.

Trials characteristics of steroid sparing agents in GCA

One of the first reports suggesting a possible steroid saving effect was published by De Silva and Hazleman in 1986. The authors used azathioprine (AZA) as a steroid sparing agent. In their cohort of 31 patients, 11 with GCA were included, 5 randomized to AZA and 6 to steroids alone (4). The conclusion was that AZA was steroid sparing after 52 weeks.

This study was followed by another preliminary report on another drug, by Krall *et al.* in 1989. The authors reported on 3 patients needing high doses of corticosteroids (40-60 mg/day) that could be

tapered to lower doses of prednisone with the addition of methotrexate (MTX) (7.5-12.5 mg/week).

The possibility that MTX could indeed be a steroid-sparing drug was confirmed in an open study by Hernandez-Garcia *et al.* (6). These authors reported that 10 out of 11 patients treated with 10 mg/week could stop the steroids within 6 months. Most importantly, the mean cumulative dose of steroids was 3.4 ± 1.03 g. Two years later Van der Veen *et al.* (7) performed a study in PMR/GCA (6 patients with GCA out of 40 with PMR). They reported negative results with MTX at the daily dose of 7.5 mg/week, but the final data were biased by a surprisingly high drop-out rate (47.5% of the whole population).

In GCA an attempt was made to reduce the final amount of steroids with cyclosporin (CsA). It was only Schaufelberger *et al.* (8) to randomize 22 patients with GCA lasting for a mean period of 39 months (range 12-72), still requiring more than 5 mg of prednisone /daily, to CsA 2 mg/kg/day. Given the biology of the disease, the rationale for giving CsA is quite strong (9,10). Yet their results were negative after 6 months. No steroid sparing effect could be shown. This appears quite surprising when taking into account the biological bases of the disease provided by several studies performed by Weyand *et al.* in which a clear TH1 milieu was demonstrated. It might well be that only an early intervention can really shut down the T cells recruited around the activated antigen-presenting macrophages, or that the actual dose of CsA was too low to obtain any noticeable effect. In fact, no through-blood level was reported, nor was any attempt to increase the dose reported. Other studies presented only in preliminary form do not improve our knowledge, and do not provide clearer evidence to prove or disprove the possibility of sparing steroids or shortening the period of treatment with any drug in GCA.

Trials in PMR

More data are available for PMR, both in terms of patients followed in the various studies and in terms of the length of the follow-up. The first report suggesting that an alternative approach might allow a more rapid control of disease activity and in the long term a shorter period of steroid treatment, was a retrospective study by David-Chaussé *et al.* (11). The cooperative French study showed that antimalarials brought the disease under control in the majority of PMR patients within 24 months. After 36 months of follow-up, only 7.4% of the patients receiving antimalarials (125 cases) were still active versus 29% of those starting steroids alone (51 cases). The possible role of antimalarials should be strongly considered when taking into account their effects on nitric oxide, as well as their de-activating properties on monocyte-macrophages.

De Silva & Hazleman (4) gave some hints as to the possibility of reducing the overall amount of steroids with AZA. No other controlled studies have appeared in the literature with antimalarials or AZA.

In the last 4 years the feasibility of using MTX as an anti-monocyte/macrophage molecule was examined in some open and controlled studies. Until now 134 patients have been given MTX, in open or controlled studies. At least one-third of the patients reported positive results with MTX in terms of a clear decrease of the total amount of steroids given to the patients, as well as in terms of a faster control of disease activity (13-15). Some of the studies were biased by the recruitment only of patients who were poor responders to steroids at doses exceeding 20 mg/day (14). Some other studies were biased by a high drop-out rate (7), reaching levels never observed in rheumatoid arthritis. Contrariwise Ferraccioli *et al.* were able, in their patients treated very early on and prospectively assessed without drop-outs, to stop steroids in 6 out of 12 patients randomized to MTX 10 mg/w plus steroids, versus 0/12 of those randomized to steroids alone (15). These authors were also able to show that a bone-sparing effect could be seen after 12 months and that the total average amount of steroids in the group of patients receiving MTX was in the lower range giving a risk of co-morbidities, according to the Mayo Clinic results.

The results of this study were the premise for a multicenter, open, randomized trial still in progress in Italy whose aim is to establish in a larger cohort of patients, whether MTX may really have any place in the armamentarium against PMR.

Conclusions and perspectives

No clear-cut evidence exist to date on any therapeutic approach with other molecules, such as MTX, AZA or even CsA, that might allow steroid sparing over time in GCA and PMR, and a shortening of the period of treatment, thus avoiding at least some of the various side-effects produced by the steroids. We certainly need large trials in PMR, as well as in GCA, randomized and analyzed on an intention-to-treat basis, to draw any firm conclusions. At this moment the strongest evidence appears to be in favour of MTX, at least in a subset of patients with early PMR. Other approaches that will soon be available in the market might offer new clues. Leflunomide (16) and mycophenolate (17), on one hand, and biologicals such as TNFrFc (18) on the other, have strong pharmacologic properties for possible employment in PMR/GCA as shown in other chronic inflammatory diseases. A better quality of life without the co-morbidities caused by long periods of steroid therapy is eagerly awaited.

We certainly support the need for a major advance in the therapeutic armamentarium beyond steroids in GCA, because we agree on the major toxicity of the steroids in the medium and long term. But in PMR, should we really ask for something better when some opinion leaders believe that at least a subset of patients may have an extraarticular inflammatory disorder? Should we first try to clarify the biological basis for the subsets of PMR, and then focus on a possible therapeutic target? In the meanwhile a straight, strong anti-osteoporotic protection should certainly be offered to all the patients receiving steroids in PMR. In fact we do not know how long our program will eventually last.

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