The COBRA trial 20 years later

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ABSTRACT

This article provides a perspective on the immediate and follow-up results of the COBRA trial that compared the combination of step-down prednisolone, methotrexate and sulfasalazine with sulfasalazine monotherapy in early rheumatoid arthritis (RA). The combination provided immediate relief of symptoms and signs of RA, but the clinical benefit compared to monotherapy appeared mostly dependent on low-dose glucocorticoid therapy that was mandatorily discontinued after 28 weeks. Strong benefit was apparent in the slowing of joint damage progression, and this effect persisted for over 10 years despite uncontrolled therapy after the trial period. In the trial toxicity of COBRA was less than monotherapy, and long-term safety of the regimen was comparable to regimens that do not include glucocorticoids. COBRA was the first study to validate the 'reverse-pyramid' concept in RA, and helped to establish the idea of a window of opportunity where the prognosis of RA may be altered with early and intensive therapy. Subsequent studies have shown COBRA is feasible in practice, acceptable to patients, and has efficacy similar to the combination of TNF inhibition and high-dose methotrexate, at a fraction of the cost.

History and context

Rheumatology has been transformed in the last decades, and I have been fortunate to be a part of this process in my professional career. When I started rheumatology training in 1986, sulfasalazine and methotrexate had been rediscovered, and were being tried as replacement for injectable gold. Treatment for rheumatoid arthritis (RA) still followed the traditional pyramid approach where progressively more effective (and toxic) drugs were applied if disease severity required it. The perspective of that time was that RA does not kill, but drugs do (1). Glucocorticoids were mostly contraindicated following the experience and disillusionment in the fifties and sixties, where long-term high doses had disastrous consequences.

At the end of my training articles were beginning to appear challenging the notion that RA was mostly a mild disease that should be treated cautiously (2, 3). Then Wilske and Healey published their paradigm-changing article on reversing the therapeutic pyramid in 1989 (4). At that time I was doing MSc training in Clinical Epidemiology in Hamilton, Canada with Peter Tugwell as supervisor. Wilske and Healey inspired me to design a "reverse-pyramid" trial in RA as topic of my MSc thesis. I decided on the combination of sulfasalazine (2g/d), methotrexate (7.5 mg/w), and initially high-dose oral prednisolone. I reasoned that 60 mg/d was an acceptable dose for many other severe autoimmune diseases, and if rapidly tapered to 7.5 mg/d as the effect of the other two drugs kicked in, side effects would be limited and manageable. Nevertheless, referees for funding agencies commented that this combination would prove lethal in some patients. Interestingly, when the study was submitted for publication 6 years later, referees commented that the dose of methotrexate was too low.

Remaining under the radar in most comments on the COBRA trial is the fact that it in effect tried to answer two questions: the first, 'is it possible and safe to achieve more remissions or low disease activity in RA patients with a reverse pyramid strategy compared to the reference standard, sulfasalazine monotherapy?' The second, 'if so, is it possible to rapidly taper and withdraw prednisolone and methotrexate and retain the advantageous effects?' The pervasive fear of toxicity prompted me to design a mandatory and rapid withdrawal of prednisolone after 28 weeks, and methotrexate after 40 weeks, although they could be reintroduced in case of a severe flare. As it turned out,

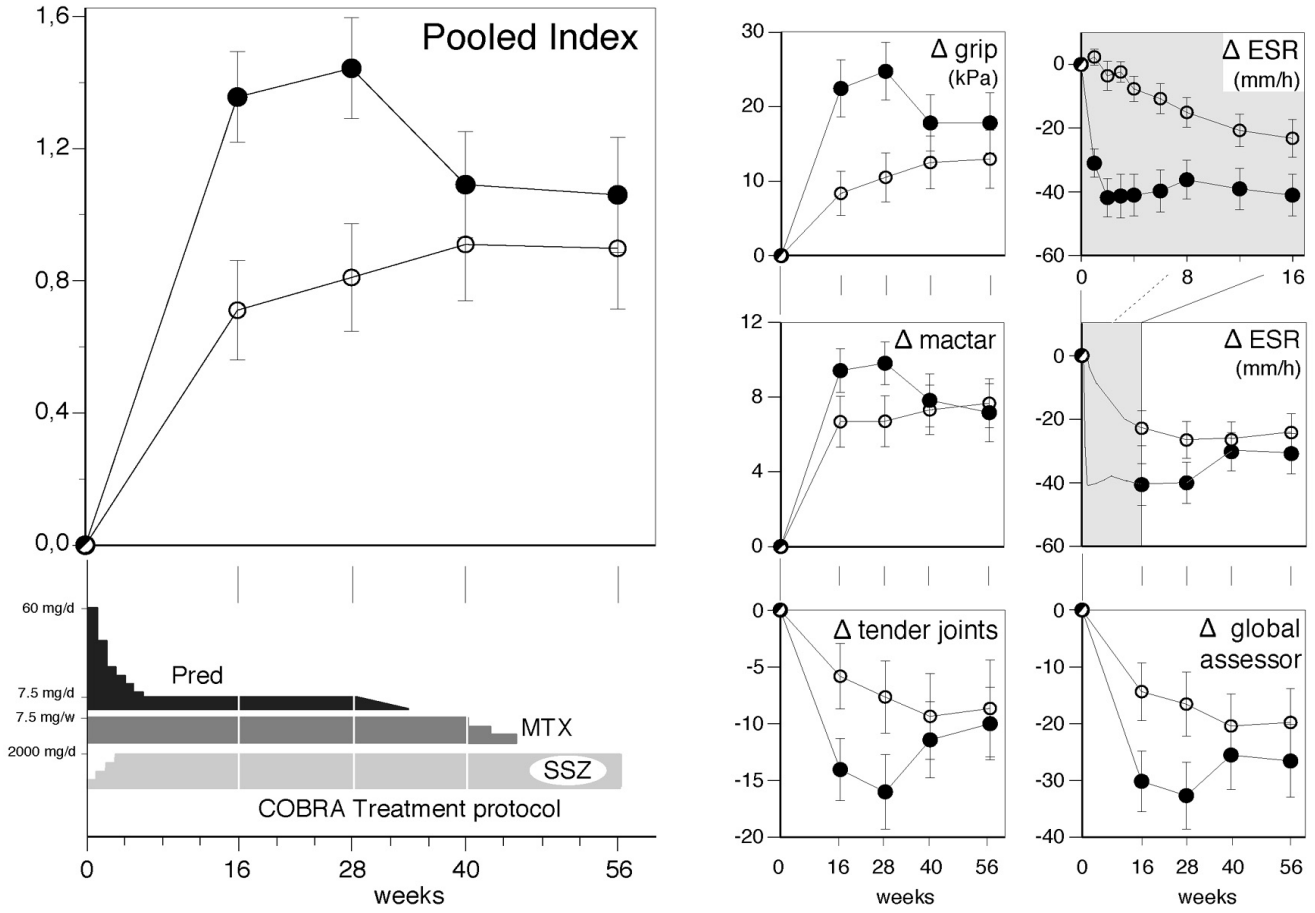

Fig. 1. Clinical outcomes of treatment, expressed as mean (95% CI) pooled index that combines the results of 5 components, shown in separate panels. Closed circles, COBRA, open circles, sulfasalazine monotherapy.
Positive values indicate improvement in pooled index, grip strength, and MACTAR (McMaster Toronto arthritis) functioning questionnaire. Negative values indicate improvement in the remaining measures. Changes in erythrocyte sedimentation rate (ESR) in first 16 weeks are shown in graph in upper right corner (note different time scale). Reprinted with permission from *Lancet*.

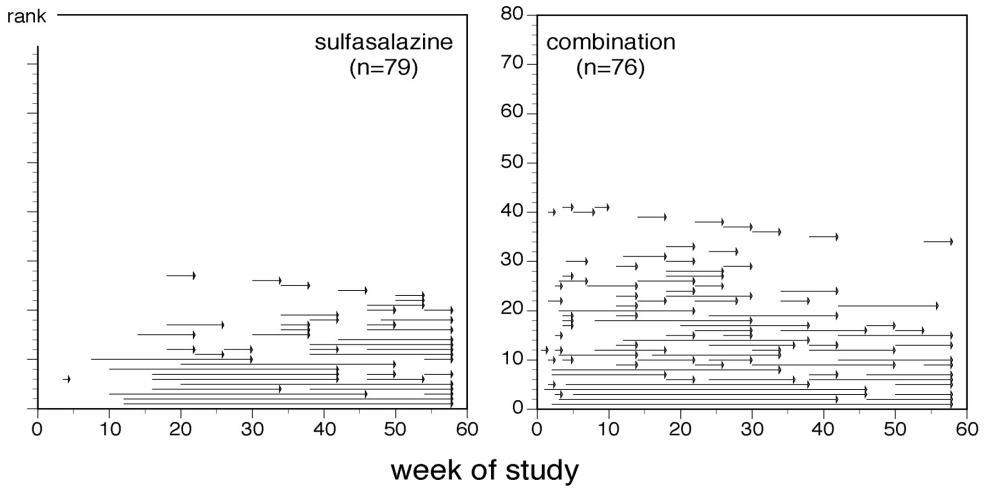

Fig. 2. Patient vector plot (28). Remission experience of all patients experiencing disease activity score remission (DAS44<1.6) at least once, ranked by total duration (lowest rank number: longest duration). All patients are represented on their own horizontal; they are in remission when the line is visible (a "vector" is drawn).

and summarised in the next section, the answer to the first question was an unequivocal 'yes', but the answer to the second was, at least for clinical disease activity, 'no'. From a huge and almost instantaneous difference in disease activity between the groups increasing up to 28 weeks, most patients on the combination experienced an increase in disease activity after tapering the combination, resulting in a loss of significance for most of the differences at the end of the trial period. Several authorities subsequently commented that the benefits of the combination were short-lived without referring to the mandatory tapering schedule.
This points to a more general feature

of the way we tend to look at glucocorticoids, something I have termed the 'dogmatic disconnect'. Most drugs are expected to show efficacy when they are administered; conversely, we expect the drug effect to disappear (or the disease to flare) when administration is stopped. This is the reason many rheumatologists continue methotrexate even in the face of suboptimal response. Uniquely, in the case of glucocorticoids we blame the drug ('short-lived effect') if the effect disappears after stopping administration. And now we know that some effects probably persist after the drug is stopped: as summarised below, long-term follow-up of patients in the COBRA trial suggests that COBRA treatment 'resets' the disease resulting in lower damage progression rates.

Trial-immediate results

The COBRA trial involved 155 early RA patients (DMARD naïve except for hydroxychloroquine in 22%; median disease duration 4 months). It compared a combination of step-down prednisolone (initially 60 mg/d, rapidly tapered to 7.5 mg/d in 6 weeks), methotrexate (at what currently is seen as a very low dose of 7.5 mg/w) and sulfasalazine (2 g/d) against the Dutch reference standard at that time, sulfasalazine monotherapy also at 2 g/d (5). For safety reasons patients were initially monitored very frequently, allowing documentation of a highly predictable and almost instantaneous effect on all parameters measured, most likely due to the glucocorticoids. For example, mean ESR was down from 55 to 23 mm/h in the first week, and at normal levels in week 2 (Fig. 1, 3). A small peak/recurrence was seen in week 8, documenting the lag time before the effects of the other two drugs started. This was also evident in the remission counts: many brief remissions, followed by 'recurrences', followed by longer lasting remission periods. (Fig. 2) The effects of sulfasalazine monotherapy were by no means insignificant, but were less and took much longer to take hold.

Interestingly, and never published before, this pattern was highly consistent across most parameters measured. Total protein decreased but albumin increased, reflecting normalisation of gamma globulin production and liver metabolism. Alkaline phosphatase decreased, probably as a result of reduced bone turnover due to suppression of inflammation. Transient changes in serum creatinine and potassium were also evident (Fig. 3). Leukocytosis was marked and followed the glucocorticoid dosing pattern; the relative distribution was altered towards polymorphs, with relative decreases in lymphocytes, monocytes and eosinophils. (Fig. 4). Platelets followed an interesting and, to my knowledge, previously undocumented biphasic response. Haemoglobin, haemtocrit and mean corpuscular volume all increased rapidly. Blood pressure was slightly higher in the COBRA group, and mean weight gain was about 3 kg, compared to 1.5 kg in the sulfasalazine group (Fig. 3), so part of the weight gain on glucocorticoid treatment should be attributed to rapid reversal of disease-induced cachexia: a beneficial effect rather than a safety issue.

As mentioned above, the favourable affects of COBRA combination therapy were strongly dependent on glucocorticoids and methotrexate. Tapering re-

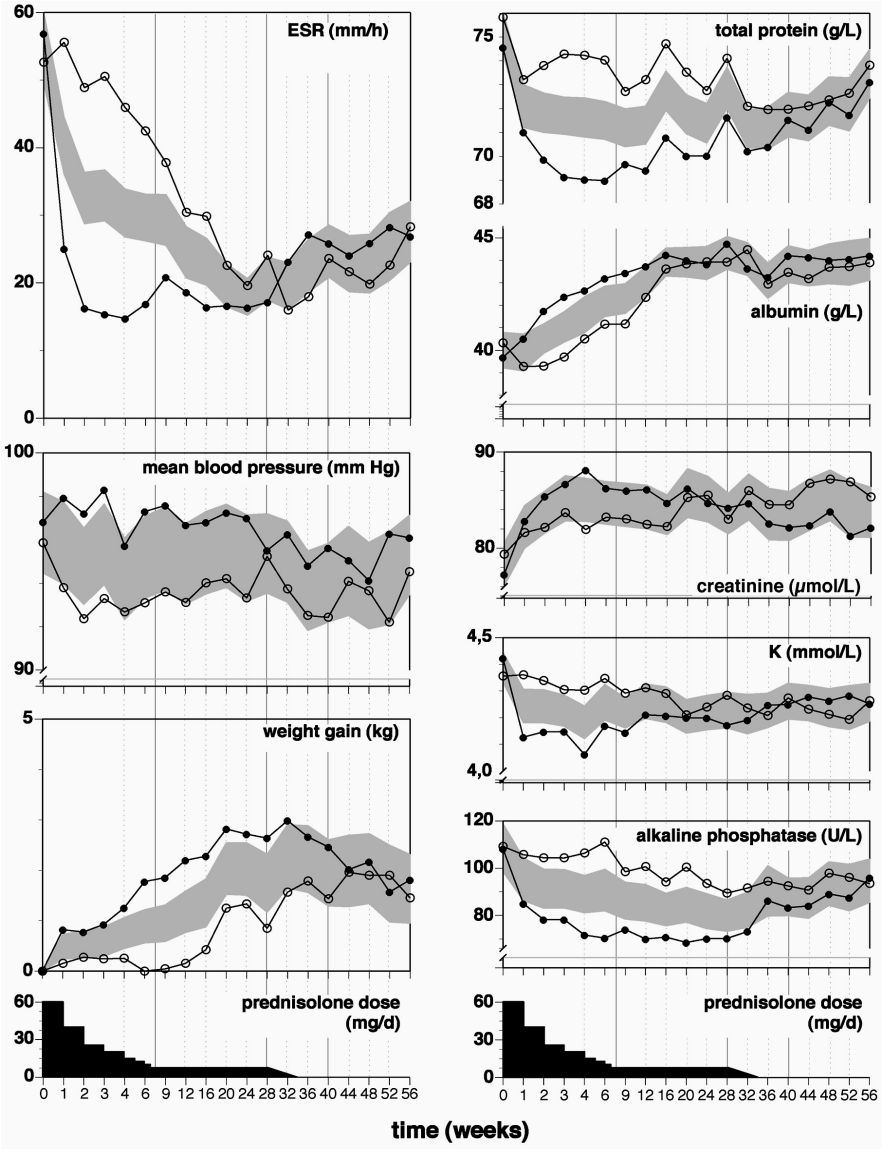

Fig. 3. Selected results of monitoring parameters. The initial period of the trial is stretched: thin vertical lines indicate 4-week periods; thicker lines indicate main outcome assessment time points. Closed circles: COBRA therapy; open circles, sulfasalazine monotherapy. The grey area between the series indicates, the 'null zone' *i.e.* the area in which the observations falls if there is no statistical difference between the groups ($p<0.05$) (27).
K: potassium; MCV: mean corpuscular volume.

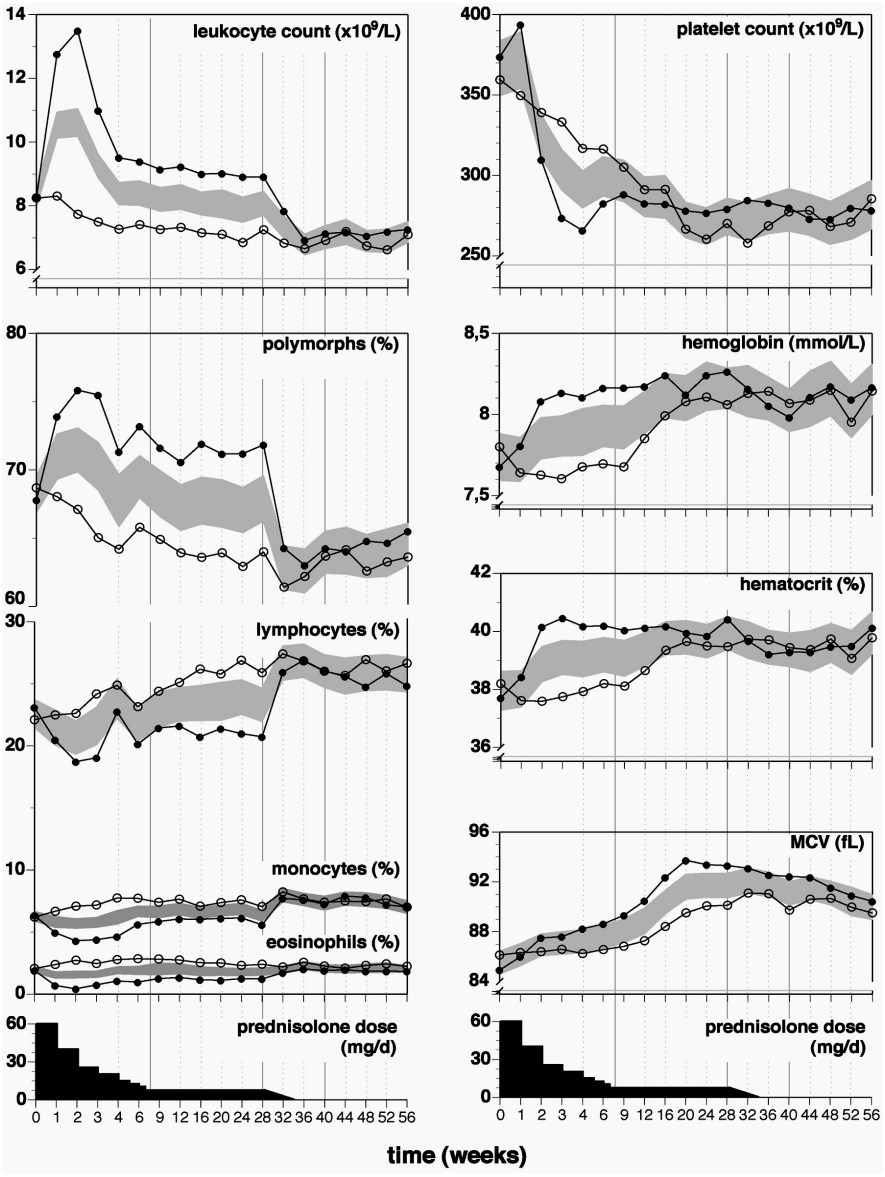

Fig. 4. Selected results of monitoring parameters, continued. Explanation, see Figure 3.

sulted in an increase of disease activity to the level of the sulfasalazine monotherapy group, although a beneficial effect on HAQ scores persisted until the end of the year.

Strong support for the inverse pyramid paradigm came from the radiographic results: COBRA progression rates were less than half that of sulfasalazine monotherapy, a result persisting until month 18 (Fig. 5). It is important to state that the radiographs were read with sequence known. This increases the sensitivity to change and leads to higher progression rates compared to reading in random sequence. Contrary to common belief, reading in sequence does not bias trial results as the higher sensitivity affects all trial groups similarly. Finally the results of the safety analysis were ground breaking: COBRA therapy resulted in much fewer severe adverse events than sulfasalazine monotherapy, for example as expressed in drug discontinuation rates. This prompted one peer reviewer to comment: "these results cannot be true because they are not logical…"

Trial-long-term follow-up

After publication of the main results we published the results of cost-effectiveness studies. As one of the first trials in rheumatology to include health economics, COBRA was found to be cost-effective and even the dominant strategy (*i.e.* more effects at lower costs) when direct and indirect costs were assessed (6, 7). Later, we were able to follow up most of the patients at about 5 and 11 years after the trial (8, 9). Our findings suggest that the difference in radiographic damage most likely increased over 11 years. In other words: effects of COBRA were still visible 11 years later, despite uncontrolled therapy after the end of the trial period! These findings must be interpreted with caution as all long-term follow-up studies necessarily suffer from weaknesses inherent in observational research. Nevertheless, the results do not support a rapid waning of effect of combination therapy.

On the safety side, the results were also reassuring, with mortality 50% less in the COBRA group (not statistically significant) and major comorbidity equally distributed among the treatment groups.

Spinoffs and implementation

COBRA has been extensively studied as arm 3 in the BeSt trial (10), where it proved equivalent to high-dose methotrexate and infliximab as described elsewhere in this issue, and in a practice setting in Belgium (11) and Bristol (12). In addition, inclusion is now complete for an Amsterdam trial that compares COBRA with 'COBRA light' a schedule that starts prednisolone at a dose of 30 mg/d, omits sulfasalazine, and applies methotrexate at 25 mg/w. First results are expected next year.

We recently completed a pilot study to compare tight control based on disease activity with control based on the levels of a bone-cartilage marker (CTX-2) (13). This study showed such control to be feasible. The most surprising finding was the effects of an intensified COBRA schedule that added hydroxychloroquine, and allowed intensification of methotrexate and the addition of anti-TNF after 5 months: 90% were in DAS28 remission (now better termed minimal disease activity) (14). This suggests there is promise of even better disease control with more intensive traditional treatment that allows an early switch to a biological agent in the case of insufficient response.

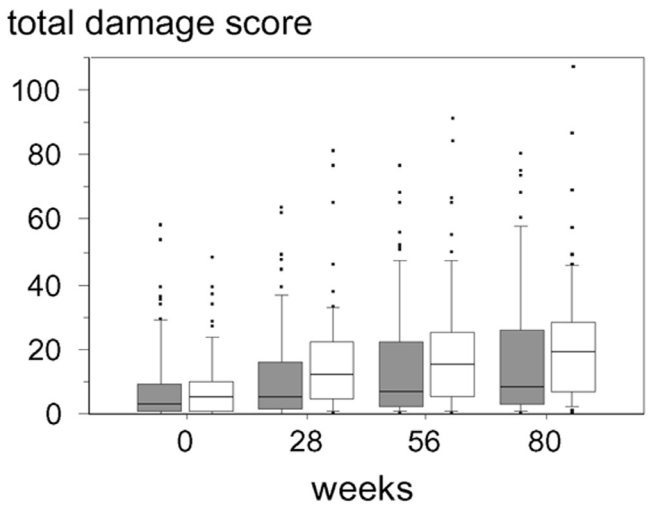

Fig. 5. Box-whisker plots of absolute radiographic damage scores (Sharp van der Heijde method; summed total scores for erosions and joint-space narrowing in hands and feet). Dark boxes, COBRA therapy; light boxes, sulfasalazine monotherapy Horizontal line in box=median; limits of box=25th and 75th percentiles; whiskers=10th and 90th percentiles; values above and below these plotted separately. Reprinted with permission from *Lancet*.

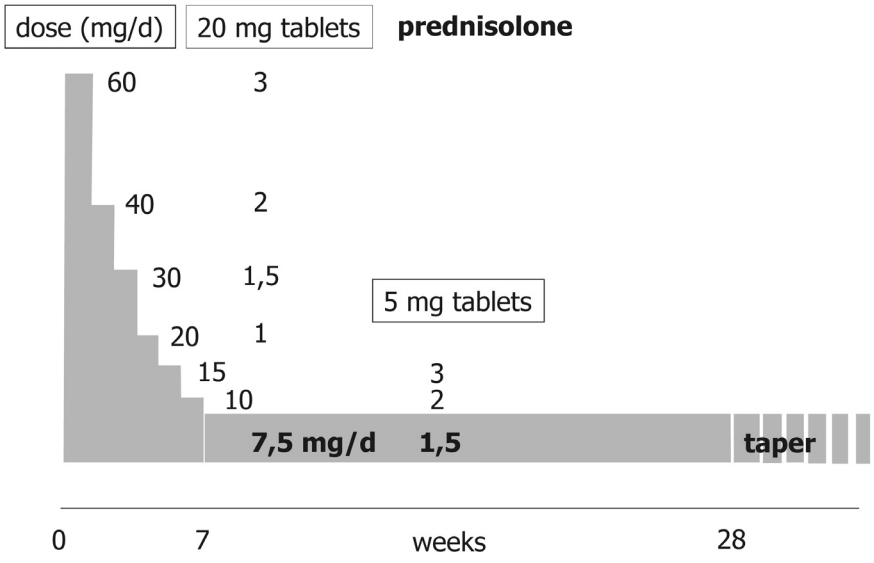

Fig. 6. Updated prednisolone step-down schedule in the COBRA strategy.

In a separate project Lilian van Tuyl wrote part of her PhD thesis on the implementation of COBRA. She found that perceptions and beliefs of Dutch rheumatologists impeded wide implementation of the schedule (15). Importantly, there were wide discrepancies between the perceptions of patients and rheumatologists. Patients were positive about aggressive regimens such as COBRA and had no qualms about taking many pills if it improved their prognosis. Rheumatologists felt the therapy to be effective and safe, but complex to administer. In addition, rheumatologists expressed concern that the patients would not be willing to take so many tablets (16). Based on these results, she developed an implementation package aimed at overcoming these barriers, including prescription packs, information booklets freely downloadable from a website accessible for both patients and physicians (see: www.cobratherapy.nl). The materials were field-tested and received positive feedback (17).

In the process, we also updated the schedule to reflect current treatment practice: we now suggest to start methotrexate at 10 mg/w, and to increase it to 25 mg/w at the first assessment for tight control, usually at 3 months. We also have simplified the step-down schedule somewhat to allow easier prescription with 20 mg tablets (Fig. 6). Also, we suggest prednisolone tapering after 6 months should be part of a tight-control strategy, *i.e.* should take place only when disease activity levels permit it, and should probably take longer than 6 weeks. In fact, as discussed elsewhere in this issue, it may be beneficial not to stop prednisolone at all, but to continue it at low doses. Finally, in view of the modern preference for methotrexate we would suggest tapering sulfasalazine as the next step if low disease activity is maintained after prednisolone has been stopped.

Finally, an unexpected benefit from the trial was the utility of the dataset for subsequent research. Stored serum samples were fully used to test various hypotheses, including some very promising studies on bone metabolism (18-24), and the ability to compare groups with different levels of response facilitated the analysis of measurement properties of many measures in use in rheumatology trials (25, 26). That such uses of the dataset were not without peril was demonstrated when, several years after the primary publication I presented a poster on a statistical analysis issue using the COBRA dataset. I was accosted by a furious American who yelled at me: "So you're the guy who's trying to kill our patients with steroids…"; an experience resembling John Kirwan's in Australia (12). Most recently, the dataset was used to help validate the new RA remission criteria (14). At the last count, at least 30 publications were directly related to the dataset. The dataset, including digitised radiographs of the complete (11-year) follow-up is still available for interested researchers.

Conclusion

COBRA was the first trial to demonstrate the benefits of the reverse pyramid strategy. Many other trials have now confirmed this, each with their own treatment strategy. Although some regimens can do without, the addition of glucocorticoids is now firmly proved to be of benefit in early RA patients. Most authors in this supplement favour a low dose. I strongly believe in the COBRA regimen, a feasible strategy with unsurpassed efficacy and low toxicity, at a par with anti-TNF but for a fraction of the cost.

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