The Computer-Assisted Management in Early Rheumatoid Arthritis programme tool used in the CAMERA-I and CAMERA-II studies

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ABSTRACT

The history, issues and result of the development of the computer decision software tool used for the two tight control and treat-to-target CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) studies are described. The software tool is simple and can be used with various protocolled strategies and visit intervals both in clinical trials and daily practice, because it does not dictate strategy steps and is independent of visit intervals. The tool gives information on whether enough improvement since the last visit is present and whether there is remission or not. With this information, strategy steps according to various protocols and treatment arms can be taken.

Introduction and history

Over the past decennia, paradigms for the treatment of early rheumatoid arthritis (RA) have changed markedly. Up till the 1980s, the paradigm was to first start after diagnosis with a non-steroidal anti-inflammatory drug (NSAID) and if insufficiently effective, to add a disease-modifying anti-rheumatic drug (DMARD). The DMARD of choice back then often was hydroxychloroquine, because of its safer adverse effects profile compared to those of the more potent d-penicillamine, azathioprine and injectable gold salts. This strategy with a basis of NSAIDs for all patients and DMARDs for the group that needed it, was called the pyramid strategy. Injectable gold salts and d-penicillamine had potentially lethal adverse effects, like aplastic anaemia and nephritis. Therefore, a generally held opinion was that this DMARD use should be initiated only when there was radiographic evidence of joint erosions, as proof of destructive RA. Use of methotrexate (MTX) in clinical practice started around the mid-1980s and became more prominent, particularly in Europe, since the mid-1990s.

The Utrecht Rheumatoid Arthritis Cohort study group consisting of Dutch rheumatologists from the University Medical Center Utrecht (UMCU) and general hospitals cooperating with the UMCU performs since 1990 treatment strategy trials in early RA. This initiative started with the clinical observation that many established RA-patients at that time eventually needed joint replacements and got wheel chair bound. The idea was that joint damage had already occurred at the initiation of DMARDs according to the pyramid strategy and that the best time to reduce disease activity is prior to joint damage. One of the first trials proved that indeed an early start of a DMARD after diagnosis was more beneficial than applying the traditional pyramid model, beginning with an NSAID only (1). Another early study of our study group showed evidence that MTX produced the best results when weighing effectiveness and toxicity of the DMARDs used at that time (2). Eventually, also based on other studies, MTX was generally seen as the anchor drug for RA (3).

The next paradigm changes in treatment strategies for early RA were the tight control and treat-to-target principles, relating to treatment strategies with frequent patient visits and dose and strategy adjustments, if needed, tailored to the disease activity of the individual patient, aimed at achieving a preset level of low disease activity or, preferentially, remission, within a certain limited period of time (4). The Utrecht Rheumatoid Arthritis Cohort study group conceived one of the earliest studies on these principles, the first Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA-I) trial (5).

Its research question was whether an MTX-based tight control strategy with patient visits each month and stepping-up, if needed, would yield better results than the conventional MTX-based strategy at that time with patient visits and medication adaptations each 3 months, so not tightly controlled. Both strategy arms were aimed at remission, however, so both were treat-to-target. For this trial, we developed a computer decision software tool (programmer JWG J). This tool later also has been used for the second CAMERA study (CAMERA-II) (6), which had the research question whether prednisone would still have disease-modifying and symptom-controlling properties in early RA, as shown in another study of our centre (7), when added to a tight control MTX-based strategy aiming for remission. In CAMERA-II, for the proof of principle, the choice of 10 mg prednisone daily was based on the same dose applied in our other study (7), that clearly had shown a DMARD-effect of this dose.

Issues at development of the computer decision software tool

At the conception of the CAMERA-I study, for which no financial support was obtained, a prerequisite was that assessments of patients participating would have to be done during routine outpatient clinics by the participating rheumatologists. Furthermore, to avoid overdosing of MTX that has a lag time before the full effect is apparent (8), we decided for the protocol to not step-up the MTX dose, if at a monthly visit there was >20% improvement in disease activity with regard to the previous visit. If ≤20% improvement and no remission yet, at each visit the next strategy intensification step according protocol should be made. So, eventually, remission would be achieved. The step-up strategy consisted in both arms of initiation, at the start of the trial, of 7.5 mg of MTX orally per week; the next steps were 15, 20, 25 and 30 mg/week orally, the following step was switching the MTX application from oral administration to subcutaneous injection and the last steps consisted of adding cyclosporine in an increasing dose. As for

both arms, the treatment aim was remission (for definition, see further), both were according to the treat-to-target principle. The differences between the two arms were the evaluation frequency, once every month (the tight-control arm) and the use of the software tool versus the evaluation frequency once every three months and step-up according predefined criteria in the protocol. The first idea was to use a digital calculation programme of the disease activity score assessing 28 joints (DAS_{28}) as a tool for the participating rheumatologists, to be used in the tight control arm of CAMERA-I. DAS_{28} had actually been designed for clinical trials and the selection of 28 joints was based on data concerning which joints were most likely to change, but in daily clinical practice, DAS_{28} also was (and is) frequently used to monitor individual patients. DAS_{28} comprises a swollen joint count (SJC_{28}), tender joint count (TJC_{28}), the erythrocyte sedimentation rate (ESR), and a visual analogue scale (VAS) for global health. The reason to develop a software tool for the use of DAS_{28} was that it is not easy to quickly calculate at the outpatient clinics (DAS_{28}= 0.7Ln(ESR) + 0.0142(VAS) + $0.555\sqrt{(TJC_{28})}$ + $0.284\sqrt{(SJC_{28})}$). So, actually a software DAS_{28} calculator was made (dBASE programme language, programmed by JWG J using the software Boxer, compiled and linked to a small DOS-programme with dBASE V). On testing this software tool, clinical issues arose with regard to assessments of >20% improvement and of remission. To give one example, DAS_{28} remission could be present notwithstanding presence of 10 swollen joints of the 28 assessed, let alone presence of swollen joints not assessed for DAS_{28}, *e.g.* of the feet. It has been shown this is indeed an important, clinically relevant issue (9). Our paper on DAS_{28} as monitoring tool for disease activity of individual RA-patients describes more drawbacks (10), such as problems related to individual DAS28 components. Because in the DAS_{28} formula a tender joint has a weight of 1.95 times that of a swollen joint and because square roots are applied, three tender joints contribute more than seven swollen joints to

the overall score. Changes in the lower, clinically less relevant range of ESR (and of C-reactive protein) influence DAS28 most. So, this DAS_{28} tool was found not appropriate for our study.

The final computer decision software tool

We decided to use a more strict definition of remission, using the same variables as used for DAS_{28}, however SJC and TJC both assessing 38 joints, including ankles and feet. Remission was defined as SJC_{38}=0, and (Boolean) ≥2 out of these three criteria: TJC_{38} ≤3, VAS for global health ≤20 mm (range 0–100 mm=worst), ESR ≤20 mm/h^{1st}. In retrospect, this remission definition has some similarities with the Boolean-based remission definition published in 2011 (11). A >20% improvement was defined as >20% improvement in SJC_{38} and (Boolean) in ≥2 out of TJC_{38}, ESR, and VAS, compared to previous visit. This was one month earlier in the tight control arm of CAMERA-I and for both strategy arms in CAMERA-II. SJC_{38}, TJC_{38}, VAS and ESR were assessed at every visit; in the tight control strategy of CAMERA-I and both strategy arms of CAMERA-II, these data were entered by the rheumatologist into the final computer decision programme at each monthly visit. This programme (developed by JWG J, method as described above) then calculated whether or not there was a >20% improvement compared to previous visit and whether or not there was remission (see Fig. 1). If neither a >20% improvement or remission was present, the strategy was intensified specifically for each strategy arm, according to protocol. For the conventional strategy in CAMERA-I, dose adjustments were performed based on the opinion of the treating rheumatologist (mainly focused on the SJC_{38}) at each 3-monthly visit, while the treatment aim also was remission as defined above. The software tool saved all entered data and also the results regarding >20% improvement and remission in a dBASE-file. The entered data at the previous visit from this file were used by the programme tool to calculate whether there was >20% improvement or not; the saved data on results

Fig. 1. The CAMERA computer decision programme.

In the input section, patient number ("Patiëntnummer"), visit number ("Bezoeknummer"), tender joint count assessing 38 joints (TJC_{38}), swollen joint count assessing 38 joints (SJC_{38}), patient's global visual analogue scale (VAS) and erythrocyte sedimentation rate (ESR, "Bezinking") are imputed.

In the output section, at the arrows, the result regarding >20% improvement compared to previous visit one month earlier ("Tov vorig bezoek 20% beter") is given as yes ("ja") or no ("nee"), and whether there is remission ("Remissie") yes ("ja") or no ("nee").

>20% improvement was defined as >20% improvement in SJC_{38} and (Boolean) >20% improvement in ≥2 out of these three: TJC_{38}, ESR, and VAS.

Remission was defined as SJC_{38}=0 and (Boolean) ≥ two out of this three criteria: TJC_{38} ≤3, VAS ≤20 mm, ESR ≤20 mm/h[1st]. On these results, protocolised strategy steps were taken. Programmer: JWG J.

regarding >20% improvement and remission enabled a check of whether indeed the right protocol steps had been taken.

Experiences with the computer decision software tool

For both the CAMERA-I and CAMERA-II studies, the tool was used in outpatient clinics in 6 and 7 hospitals, respectively and by usually more than one rheumatologist at each centre, without any problems. Eventually, when work stations not allowing usage of other than standard software were introduced, the author had to contact the Information and Communication Technology departments of the respective hospitals to enable usage of the tool, which proved to be no problem. After the CAMERA-studies, there were rheumatologists who expressed the wish to use the tool also for routine daily clinical practice of patients with early RA, because they liked it.

In the meantime, we made a similar Access programme tool, which was not used however in the following trial, *i.e.* UActEarly (12), in which also a stricter than normal DAS28 remission definition was chosen (DAS28<2.6 and (Boolean) a swollen joint count ≤4), and in which at each month according protocol intensifying strategy steps were taken, if remission was not yet achieved.

We concluded from the CAMERA-I trial that tight control treatment with MTX, aiming for remission, resulted in a better outcome over two years compared to a not tight control treatment as was the standard at that time, and that the computerised decision programme was a helpful tool, which also could be used in daily clinical practice. From CAMERA-II it was additionally concluded that prednisone 10 mg daily, added for 2 years to a tight control MTX-based strategy aiming for remission in early RA, still had disease modifying and symptom controlling properties, with less adverse effects in the added prednisone strategy, due to less high MTX-dosages needed, and

with less patients having to initiate additional biological DMARD therapy.

With the basic principles of the CAMERA decision software tool, Apps could be developed to be generally used on tablets or smartphones for daily clinical practice for treat to target strategies in early RA, as the App would be independent of the frequency of visits of patients and of specific treatment strategies and strategy steps, which could be dictated by protocol or international guidelines. As such, the App would meet the unmet need of a tool that could be used in individual patients to monitor RA disease activity while implementing the treat-to-target principle in daily clinical practice.

Conclusion

The CAMERA studies applying a feasible, simple and face valid computer decision programme tool have been successfully conducted, and they showed good results of tight control treatment of early RA patients with conventional anchor drugs, aiming for remission.

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