Clinical Immunology 186 (2018) 74–78

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

What have we learned from BeSt?

Cornelia F. Allaart *, Iris M. Markusse, Willem F. Lems

Leiden University Medical Center, Netherlands

ARTICLE INFO

Article history:
Received 14 September 2017
Accepted with revision 15 September 2017
Available online 18 September 2017

ABSTRACT

Background: How have the long term outcomes of RA improved in the last decade?
Methods: Patients with DMARD naïve RA were randomized to 4 treatment strategies: 1. sequential DMARD monotherapy, 2. step-up combination therapy, 3. initial combination therapy including prednisone or 4. including infliximab. Treatment-to-target was aimed at DAS ≤ 2.4 (three-monthly calculations). Functional ability (HAQ), radiologic damage progression (Sharp/vanderHeijde Score) and overall survival were reported.
Results: Patients in arms 3 and 4 showed earlier clinical improvement. Up to 50% achieved DAS-remission (<1.6), up to 29% achieved drug free remission. Damage progression was well suppressed (median after 10 years in completers 2 SHS points), functional ability approached normality (mean HAQ 0.6). There was no increased mortality (Standardized Mortality Ratio 1.16, 95% CI 0.92–1.46).
Conclusions: Early treatment determines early clinical improvement, treatment-to-target determines long term outcomes. Prevention of relevant radiologic damage progression and disability, drug free remission and normalized survival are realistic goals.

1. Introduction

For many years, rheumatoid arthritis has been associated with prolonged, painful inflammation, progressively debilitating joint damage and increased mortality. Therapies were often introduced late, feared for potential side effects, and/or ineffective. However, from the late 1990s, more disease modifying antirheumatic drugs (DMARD) and drug combinations became available, and rheumatologists in the Netherlands wondered which would be the best order to use them: start with 'cornerstone' methotrexate (MTX) and possibly other monotherapies and reserve combination therapy with prednisone or infliximab for patients who did not respond sufficiently well, or start with combination therapy and taper to monotherapy when possible? This was addressed in a four-armed treatment strategy study (BeSt, acronym of the Dutch for 'Treatment Strategies'), with arms 1 and 2 starting with MTX monotherapy (switching to or adding other DMARD), and arms 3 and 4 starting with combination therapy, either with prednisone (arm 3) or infliximab (arm 4) [1].

Previously, in the TICORA study it had been shown that functional ability and radiologic damage progression outcomes were better if the decision to intensify treatment was based on calculation of the Disease Activity Score rather than on interview based evaluation of disease activity [2]. Thus, in the BeSt study, three-monthly calculated DAS [3] were used to determine whether treatment had to be intensified.

To prevent over-treatment, since initial combination therapy starters in theory could have responded well to monotherapy, also tapering strategies were designed, if the treatment target of low DAS was achieved for at least 6 months. When it was found that many patients had achieved DAS-remission even after tapering, from year 3 discontinuation of the last DMARD was introduced in the study protocol, resulting in patients achieving drug free remission.

2. Results

Of 508 patients with recent onset active (at least 6 of 66 joints swollen and 6 of 68 tender, and either an ESR of 28 or higher or a patient's VAS for disease activity of 28 or higher) RA (ACR 1987 classification criteria), 62% were still participating in the study after 10 years. Early improvement had occurred more often in the initial combination therapy arms [4]. But as a result of DAS-steered treatment adjustments, by the end of year 1 and in subsequent years, similar percentages of patients across the four arms had low disease activity and DAS-remission, and functional ability over time was similar and stable, approaching normality as reported in a 55-plus general population [5].

Discontinuation of all DMARD because of prolonged DAS-remission had occurred in 26% of all patients without differences between the strategy arms ($p = 0.57$). By the end of year 10, 11/109, 11/104, 12/109 and 13/107 patients in arms 1–4 were still in drug free remission, with a median duration of 25, 75, 38 and 68 months, respectively ($p = 0.27$). Over time due to DAS steered treatment, patients in all arms had gone through 4 treatment steps. Only 17% in arm 1, 11% in arm 2,

* Corresponding author.
E-mail address: c.f.allaart@lumc.nl (C.F. Allaart).

https://doi.org/10.1016/j.clim.2017.09.017

25% in arm 3 and 41% in arm 4 were still on the initial treatment step, which for patients in arms 3 and 4 meant they had tapered to monotherapy or drug free remission [6].

Disease flares defined by DAS increase to >2.4, occurred in most patients at least once, with a decreasing prevalence over time [7].

Only 25% of flares were preceded by drug tapering. Flares were associated with an increase in HAQ at the time of flare, but also with a higher mean HAQ and more SHS progression over time.

Joint damage progression after 10 years of DAS-steered treatment was low: median 2 points on the Sharp/van der Heijde score, without

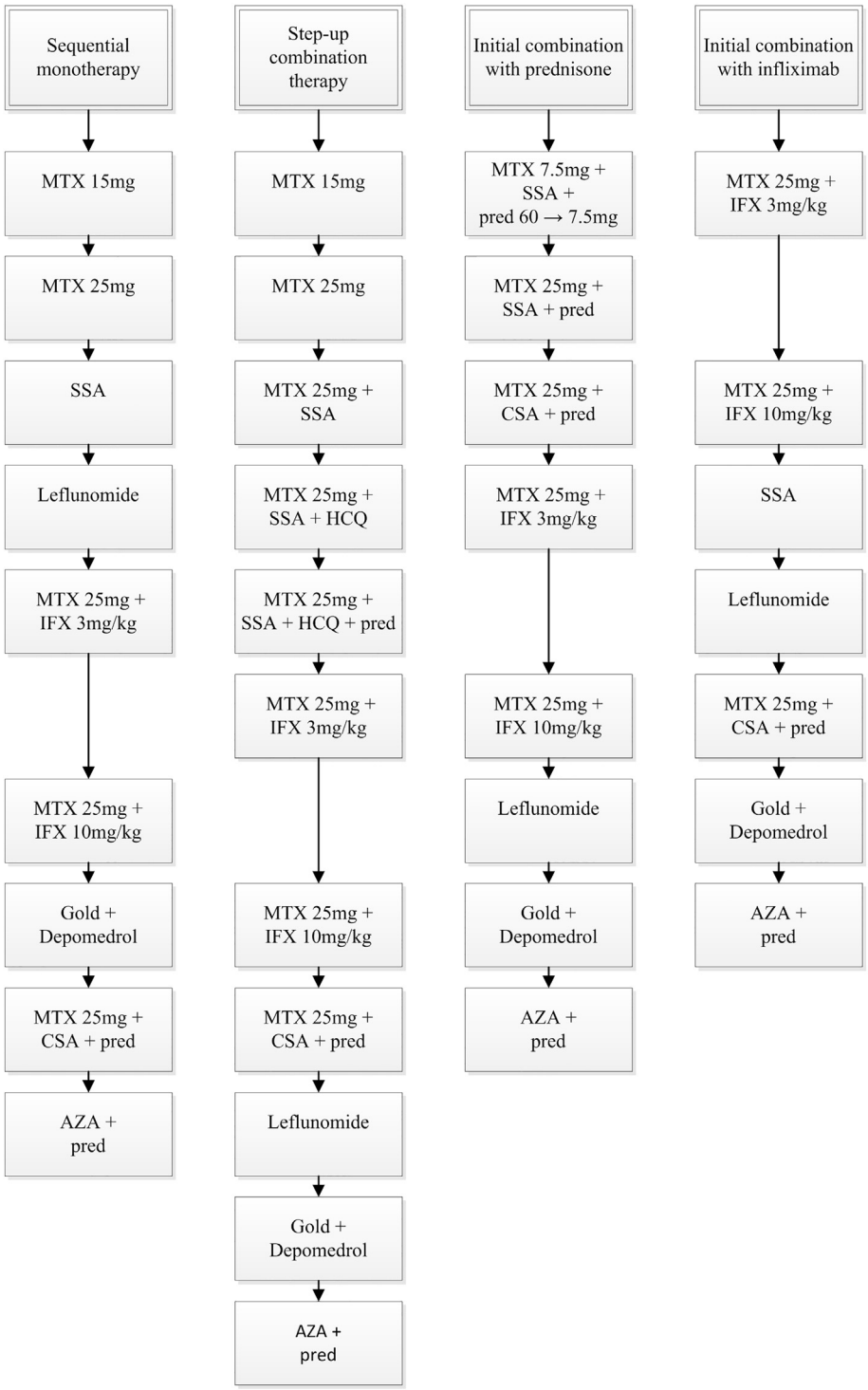

Fig. 1. Flow diagram of the treatment strategies, showing required treatment intensification steps as long as three-monthly measured DAS remained >2.4. Note 1: In all strategy arms, different patients may progress from one treatment step to the next over different time intervals, depending on individual DAS results at the three-monthly observations. Note 2: Patients on infliximab (dosed at 8–weekly intervals) had additional DAS measurements one week before each next infusion. That DAS dictated if the infliximab dose would need to be increased. Infliximab dose started with 3 mg/kg and, if DAS > 2.4, was stepwise be increased to 6 mg/kg, 7.5 mg/kg and finally 10 mg/kg (always rounded to the nearest hundred). Tapering of the dose could go in reverse order if three-monthly DAS calculations were ≤2.4 for at least 6 consecutive months. AZA, azathioprine 2-3 mg/kg/day; CSA, ciclosporin A 2.5 mg/kg/day; Depomedrol, 3 gifts of 120 mg in week 1, 4 and 8; Gold 50 mg/week; HCQ, hydroxychloroquine 200 mg/day, IFX, infliximab, dosages once per 8 weeks; Leflunomide 20 mg/day; MTX, methotrexate, dosages per week; Pred, prednisone 7.5 mg/day unless indicated otherwise; SSA, sulphasalazine 2000 mg/day.

differences between the arms. In particular in the first years of the study, there had been statistically significantly less damage progression in arms 3 and 4 [1,8]. Over time, the mean estimated SHS progression was still statistically, but not clinically relevantly less in arm 4 compared to the other arms: 10.9, 8.4, 8.1, and 6.1 for strategies 1 to 4, respectively (weighted GEE, P = 0.15 for overall comparison; P = 0.046 for strategy 1 vs. 4; P > 0.10 for other comparisons) [6].

Over 10 years follow up, there were a similar number of adverse events in the strategy arms (74 per 100 patients' years, p = 0.159). Frequencies of serious adverse events vary over time, without significant differences between the arms [6]. Seventy-two patients died during follow-up. Based on the general Dutch population, 62 would have been expected, which results in a Standardized Mortality Ratio of 1.16 (95% confidence interval 0.92–1.46), without differences between the strategy arms, indicating no increased mortality in the BeSt study population.

3. Discussion

The BeSt study has shown that the long-term outcomes of patients with RA have greatly improved in the last decades. The introduction of new (combinations of) antirheumatic drugs has given rheumatologists more options to treat patients better, intensifying and changing treatment as long as disease activity is insufficiently suppressed. After 10 years of DAS-steered treatment there are few patients with clinically relevant joint damage progression, many patients in clinical remission, and even patients in prolonged drug free remission. Survival in this cohort was comparable to that of the general population. The debilitating, destructive, deadly disease that rheumatoid arthritis was for so many patients in the past, appears to have been tamed at last.

Given the design of the study, and the previous results of the TICORA trial, it is very likely that the good long term outcomes are due to continued three-monthly DAS calculations and treatment adjustments aiming at DAS ≤ 2.4. 'Treatment to target' is now incorporated in daily practice in most rheumatology clinics. To date, based on both theory and the results of the remission steered FINRA-Co study [9] and CAMERA study [10], remission is the preferred target [11].

If rheumatoid arthritis is seen as a chronic, progressively worsening disease, it is reasonable to compare the efficacy of therapies and treatment strategies in terms of long term outcomes. The results of the BeSt study show that the long term outcomes are less dependent on the use of particular DMARDs than on treatment to target. However, treatment of RA is not only a marathon, it is also a sprint. Early suppression of inflammation is important to alleviate symptoms and return patients to their normal way of life as much as possible. It will also help to install hope and faith in the patient as well as the physician, motivating both to continue following the treatment to target protocol [12]. Patients in arms 3 and 4 reported earlier functional improvement and

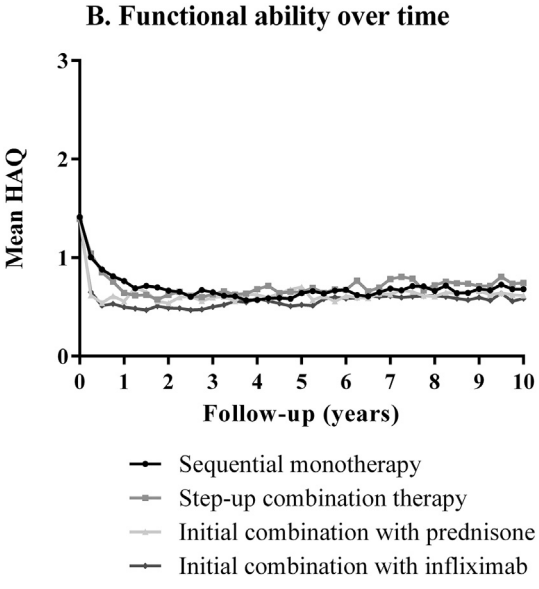

Fig. 2. Mean functional ability over time (based on estimates of a linear mixed model).

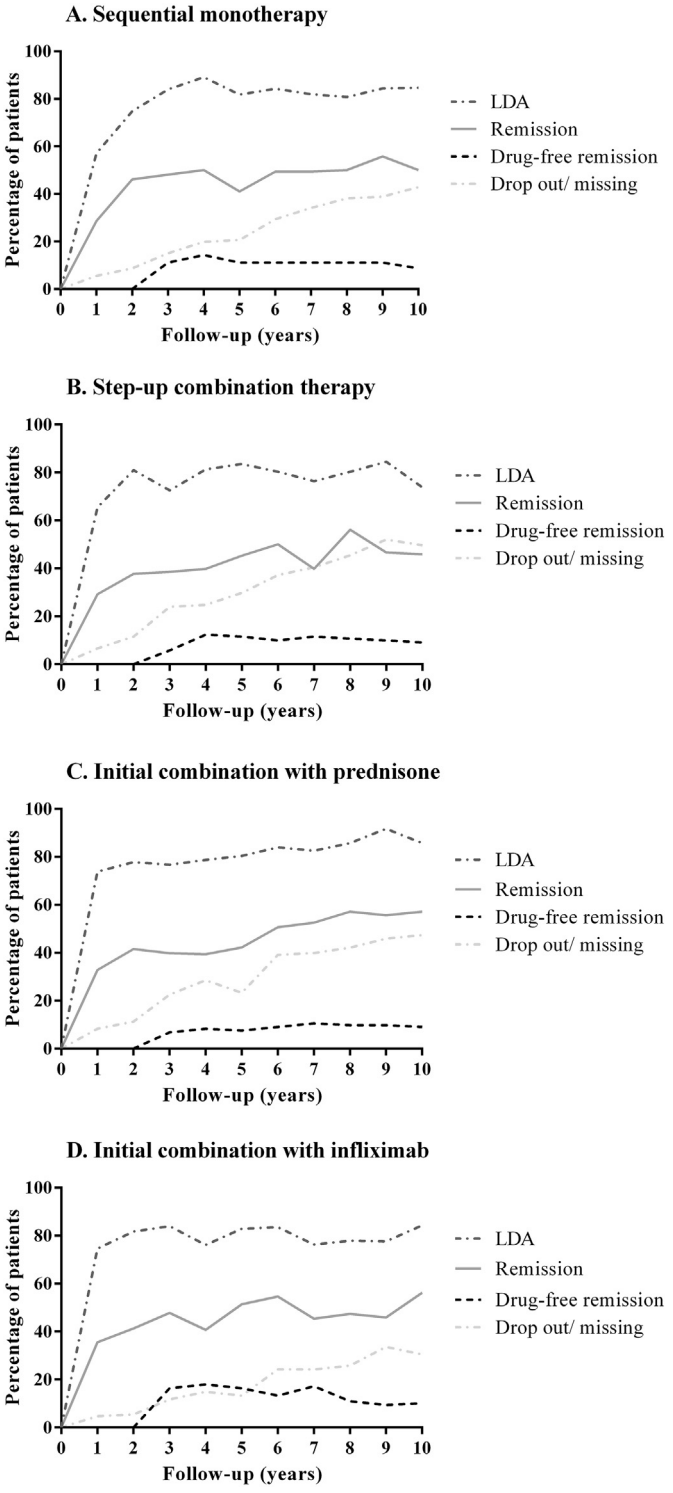

Fig. 3. Patient disposition over time (observed data, showing the percentage of total number of patients included, not of total number of patients with data available at that timepoint) for patients allocated to (A) sequential monotherapy, (B) step-up combination therapy, (C) initial combination with prednisone and (D) initial combination with infliximab. LDA, low disease activity (defined as DAS ≤ 2.4).

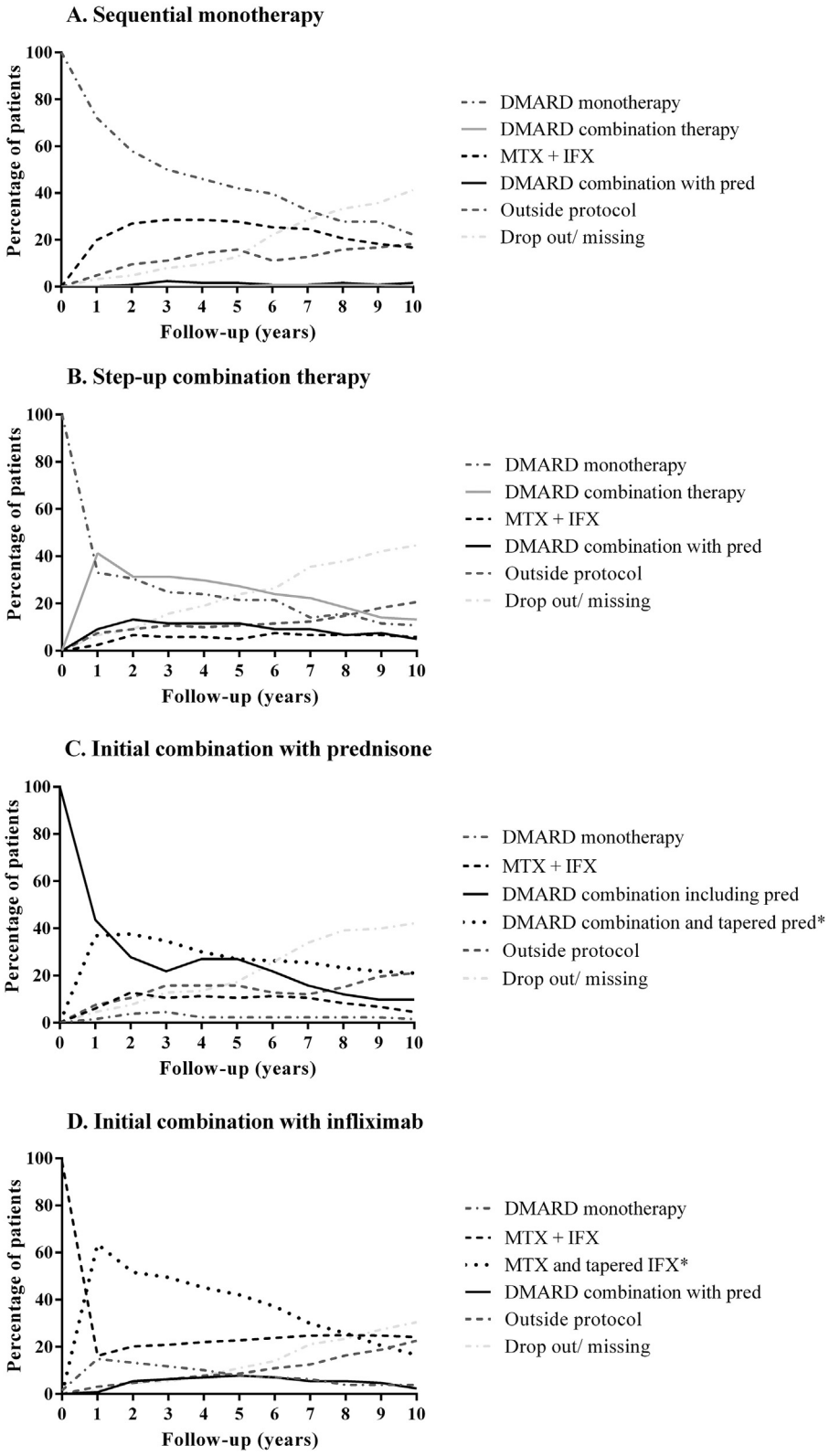

Fig. 4. Percentages of patients on various treatment steps over time for patients allocated to (A) sequential monotherapy, (B) step-up combination therapy, (C) initial combination with prednisone and (D) initial combination with infliximab. *These lines in strategy arm 3 and 4 depict the number of patients on the initial treatment step who have tapered to monotherapy or discontinued all medication. Note 1: Outside protocol denotes patients who, although continuing DAS ≤ 2.4 steered treatment, did not use medications of the sort and/or at the time required in the protocol. Note 2: Comparison of patients still on the initial treatment step at year ten: $p < 0.001$ for strategy arm 1 versus strategy arm 4; $p < 0.001$ for strategy arm 2 versus strategy arm 4; $p = 0.002$ for strategy arm 2 versus strategy arm 3; $p = 0.038$ for strategy arm 3 versus strategy arm 4; other comparisons not significant. Note 3: 47 patients in drug-free remission at year 10 achieved this (i.e. achieved and maintained remission allowing to taper to drug-free) on the following treatment steps: methotrexate monotherapy, 13/47 (28%) (for all the initial treatment step in strategy arm 1 and 2); methotrexate and infliximab, 11 (23%) (for all the initial treatment step in strategy arm 4); methotrexate, sulphasalazine and prednisone, 8 (17%) (for all the initial treatment step in strategy arm 3); methotrexate with sulphasalazine, 4 (9%); sulphasalazine monotherapy, 2 (4%); leflunomide monotherapy, 2 (4%); methotrexate, ciclosporin A with prednisone, 2 (4%); methotrexate with sulphasalazine and hydroxychloroquine, 1 (2%); azathioprine with prednisone, 1 (2%); outside protocol, 3 (6%). DMARD, disease-modifying antirheumatic drug; IFX, infliximab; MTX, methotrexate.

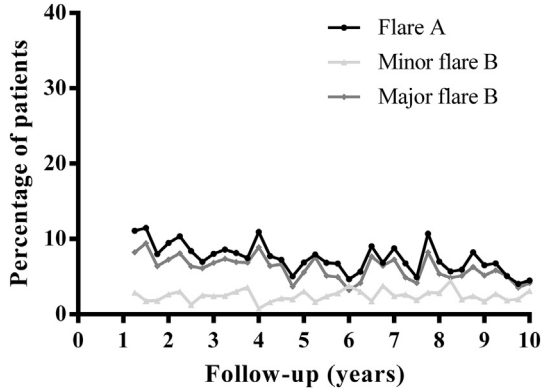

Fig. 5. Percentage of patients with a flare per performed visit over time. Flare A: from any DAS to DAS > 2.4 with an increase in DAS of ≥ 0.6; minor flare B: from DAS ≤ 2.4 to DAS > 2.4 with an increase in DAS of < 0.6; major flare B: from DAS ≤ 2.4 to DAS > 2.4 with an increase in DAS of ≥ 0.6. Note, flares are defined from year 2 to year 10.

other patient reported outcomes [13], better quality of life and, particularly in arm 4, more sustained work productivity in the first 2 years of the study, compared to patients in arms 1 and 2 [14]. Early suppression of inflammation is also associated with prevention of rapid radiologic progression [15]. However, with continued treatment to target, in the majority of patients radiologic damage progression was not associated with a clinically relevant decrease in HAQ [16] (Figs. 1–6).

In conclusion, the BeSt study has shown that long term outcomes are more dependent on treatment to target, resulting in little damage, normalized ability and normal survival, but that the initial treatment determines the early response. Initial combination therapy with prednisone or infliximab is most effective to achieve rapid suppression of disease activity and can then often be tapered to monotherapy. Remission and drug free remission can be achieved and appear realistic treatment targets. Since the end of the BeSt study, new treatment combinations and antirheumatic drugs have been introduced for the treatment of RA. New studies have been initiated, aiming at ever earlier treatment initiation, and aiming at ever stricter remission outcomes. It is possible that these endeavours will lead to the best outcome of all: a cure for RA.

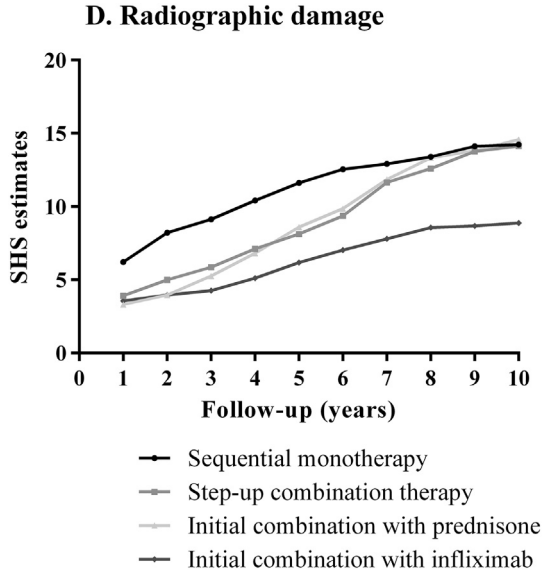

Fig. 6. Estimated radiographic damage (weighted generalized estimating equation), during/after ten years of targeted treatment, with multiple medication adjustments when low disease activity was not achieved or maintained, for the four treatment strategies. Depiction of SHS estimates over time for the total BeSt population, as a result of the weighted generalized estimating equation.

Financial disclosure

The BeSt study was sponsored by a government grant of the Dutch College of Health Insurances (OG99-026), and received financial support from Schering-Plough/Centocor/Janssen.

References

[1] Y.P. Goekoop-Ruiterman, J.K. de Vries-Bouwstra, C.F. Allaart, D. van Zeben, P.J. Kerstens, J.M. Hazes, et al., Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial, Arthritis Rheum. 52 (11) (2005) 3381–3390.
[2] C. Grigor, H. Capell, A. Stirling, A.D. McMahon, P. Lock, R. Vallance, et al., Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial, Lancet 364 (9430) (2004) 263–269.
[3] D.M. van der Heijde, M. van t Hof, P.L. van Riel, L.B. van de Putte, Development of a disease activity score based on judgment in clinical practice by rheumatologists, J. Rheumatol. 20 (3) (1993) 579–581.
[4] Y.P. Goekoop-Ruiterman, J.K. de Vries-Bouwstra, C.F. Allaart, D. van Zeben, P.J. Kerstens, J.M. Hazes, et al., Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial, Ann. Intern. Med. 146 (6) (2007) 406–415.
[5] E. Odding, H.A. Valkenburg, D. Algra, F.A. Vandenouweland, D.E. Grobbee, A. Hofman, Association of locomotor complaints and disability in the Rotterdam study, Ann. Rheum. Dis. 54 (9) (1995) 721–725.
[6] I.M. Markusse, G. Akdemir, L. Dirven, Y.P. Goekoop-Ruiterman, J.H. van Groenendael, K.H. Han, et al., Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: a randomized trial, Ann. Intern. Med. 164 (8) (2016) 523–531.
[7] I.M. Markusse, L. Dirven, A.H. Gerards, J.H. van Groenendael, H.K. Ronday, P.J. Kerstens, et al., Disease flares in rheumatoid arthritis are associated with joint damage progression and disability: 10-year results from the BeSt study, Arthritis Res. & Ther. 17 (2015) 232.
[8] N.B. Klarenbeek, M. Guler-Yuksel, S.M. van der Kooij, K.H. Han, H.K. Ronday, P.J. Kerstens, et al., The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study, Ann. Rheum. Dis. 70 (6) (2011) 1039–1046.
[9] T. Sokka, H. Makinen, K. Puolakka, T. Mottonen, P. Hannonen, Remission as the treatment goal–the FIN-RACo trial, Clin. Exp. Rheumatol. 24 (6 Suppl. 43) (2006) S-74–6.
[10] S.M. Verstappen, J.W. Jacobs, M.J. van der Veen, A.H. Heurkens, Y. Schenk, E.J. ter Borg, et al., Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial), Ann. Rheum. Dis. 66 (11) (2007) 1443–1449.
[11] J.S. Smolen, R. Landewe, J. Bijlsma, G. Burmester, K. Chatzidionysiou, M. Dougados, et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update, Ann. Rheum. Dis. 76 (6) (2017) 960–977.
[12] I.M. Markusse, L. Dirven, K.H. Han, H.K. Ronday, P.J. Kerstens, W.F. Lems, et al., Continued participation in a ten-year tight control treat-to-target study in rheumatoid arthritis: why keep patients doing their best? Arthritis Care Res. 67 (6) (2015) 739–745.
[13] S.M. van der Kooij, J.K. de Vries-Bouwstra, Y.P. Goekoop-Ruiterman, J.A. Ewals, K.H. Han, J.M. Hazes, et al., Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis, Arthritis Rheum. 61 (1) (2009) 4–12.
[14] W.B. van den Hout, Y.P. Goekoop-Ruiterman, C.F. Allaart, J.K. de Vries-Bouwstra, J.M. Hazes, P.J. Kerstens, et al., Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis, Arthritis Rheum. 61 (3) (2009) 291–299.
[15] K. Visser, Y.P. Goekoop-Ruiterman, J.K. de Vries-Bouwstra, H.K. Ronday, P.E. Seys, P.J. Kerstens, et al., A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study, Ann. Rheum. Dis. 69 (7) (2010) 1333–1337.
[16] M. van den Broek, L. Dirven, J.K. de Vries-Bouwstra, A.J. Dehpoor, Y.P. Goekoop-Ruiterman, A.H. Gerards, et al., Rapid radiological progression in the first year of early rheumatoid arthritis is predictive of disability and joint damage progression during 8 years of follow-up, Ann. Rheum. Dis. 71 (9) (2012) 1530–1533.