



Universiteit  
Leiden  
The Netherlands

## Targeting the humoral immune system of patients with rheumatoid arthritis

Teng, Y.K.O.

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## Chapter 10

Long-term follow-up of health status in patients with severe rheumatoid arthritis after high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation

Teng YKO\*  
Verburg RJ\*  
Sont K  
van den Hout WB  
Breedveld FC  
van Laar JM

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\*these authors contributed equally to the manuscript



## **Abstract**

### **Objective**

High-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (HSCT) is a new treatment for patients with severe, refractory rheumatoid arthritis (RA). The present study was undertaken to assess the health status of patients with severe RA over a long-term follow-up period after treatment with HDC + HSCT.

### **Methods**

Health status and utility scores were assessed in 8 patients before and after treatment with HDC + HSCT. Patients were followed up to 5 years posttransplantation. Health status was assessed by the Health Assessment Questionnaire (HAQ), the RAND-36 version of Short Form 36 (SF-36) health survey, and the Arthritis Impact Measurements Scales (AIMS). Utility scores were calculated using the EuroQol (EQ-5D) questionnaire and the SF-36-derived utility index (called the SF-6D), from which quality-adjusted life years (QALYs) were derived.

### **Results**

Most measures of health status improved compared with baseline in the first 2 years post-transplantation, notably HAQ and AIMS scores and scores on the functional status, general health, and health change summary scales of the RAND-36 version of the SF-36. Utility scores derived from EQ-5D questionnaire and the SF-6D also increased significantly after transplantation. This was reflected in the 0.28 QALYs gained compared with baseline. For a putative 50-year-old RA patient with a life expectancy of 20 years, a threshold analysis revealed that HDC + HSCT yielded more QALYs than conventional therapy when treatment-related mortality (TRM) was <2.8%.

### **Conclusion**

HDC + HSCT temporarily increased the functionality and health status of patients with severe, refractory RA. With a reported TRM of 1.3%, HDC + HSCT can be considered a realistic treatment option for patients with severe RA.

Rheumatoid arthritis (RA) is a chronic disease that results in significant morbidity, impaired quality of life, and a reduced life expectancy<sup>1,2</sup>. High-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (HSCT) is a new treatment strategy for patients with severe RA<sup>3,4</sup>. Several pilot studies have shown remarkable clinical improvement for up to 2 years in patients with previously refractory RA, as measured by Disease Activity Scores with physical examination of all 44 joints (DAS44)<sup>4,5</sup> and C-reactive protein levels<sup>4,5</sup>. Although no cure was observed, sensitivity to disease-modifying antirheumatic drug (DMARD) therapy was restored after transplantation<sup>3,4</sup>.

We previously reported a clinical decision analysis using Markov modeling to estimate quality-adjusted life years (QALYs) resulting from HDC + HSCT versus conventional therapy. The model predicted that HDC + HSCT could be superior if treatment-related mortality (TRM) remained low<sup>6</sup>. However, so far, it remains unclear whether long-term health status in patients with severe RA is actually enhanced by a treatment involving HDC + HSCT, which is important in clinical decision-making regarding the treatment of these patients.

The purpose of this study was to assess the health status of patients with severe RA over a long-term follow-up period after treatment with HDC + HSCT. In addition, we calculated the valuation of the patients' health expressed in utilities in order to establish whether HDC + HSCT results in a gain in QALYs.

## Patients & Methods

### Patient selection

Seven women and one man (mean age 43 years [range 35-51 years], mean disease duration 13 years [range 7-20 years]) were treated at Leiden University Medical Center (LUMC) with HDC + HSCT as part of a multicenter phase I/II trial<sup>6</sup>. Patients had an established diagnosis of RA according to the 1987 revised criteria of the American College of Rheumatology (formerly, the American Rheumatism Association)<sup>8</sup>, had progressively erosive disease with large joint involvement, and had disease that was refractory to DMARDs, including maximal tolerable dose of methotrexate (MTX) and combination therapy. In addition, 4 patients had disease that did not respond to tumor necrosis factor

(TNF) blockade. All patients were rheumatoid factor positive and had high DAS<sub>44</sub> scores at baseline (mean score 5.4 [range 3.82-7.24]) as defined by the criteria of the European League Against Rheumatism (EULAR)<sup>7</sup>. The protocol was approved by the Ethics Committee of LUMC, and all patients provided written informed consent.

### **Study design**

Patients were followed at 3-month intervals for the first year posttransplantation, 6-month intervals in the second year posttransplantation, and once more at 5 years posttransplantation. Clinical outcome, health status, and utility were assessed at all time points, except for the clinical outcome at 5 years.

### **Clinical outcome**

Clinical responses were categorized according to the EULAR response criteria<sup>7</sup>. Functionality was measured using the standard disability index of the Health Assessment Questionnaire (HAQ)<sup>7</sup>.

### **Health status assessments**

Health status was measured using the Arthritis Impact Measurement Scales (AIMS) and the Short Form 36 (SF-36) health survey. The AIMS is a reliable instrument, validated for use in The Netherlands as the Dutch-AIMS, which measures health status in a multidimensional manner using specific scales, summary components, and overall impact measures<sup>8</sup>. In the present study, the Arthritis Impact visual analog scale (VAS) was used because it is a good indicator of the impact of RA on patients' general health<sup>9</sup>. The RAND-36 version of the SF-36 assesses patients' health status across 9 dimensions, from which the following 4 summary scales are constructed: 1) functional status, the summary scale of physical functioning, social functioning, physical role limitations, and emotional role limitations; 2) well-being, the summary scale of mental health, vitality, and pain; 3) general health; and 4) health change<sup>10</sup>.

### **Utility and QALYs**

Utility is the valuation of a patient's health on a scale from 0 (death) to 1 (optimal health). Utilities were measured using the EuroQol (EQ-5D) questionnaire<sup>11</sup> and the SF-36-derived utility index, called the SF-6D<sup>10</sup>. In both instruments, patients describe their health status using a classification system. Utilities for

these descriptions are obtained from large representative study populations in the UK, based on a time trade-off procedure for the EQ-5D questionnaire and on a standard gamble procedure for the SF-6D<sup>12</sup>. Because sustained improvement of utility (and not the individual measurements) is important for patients, QALYs were calculated as the area under the curve (AUC) from the SF-6D utility scores of the patients who underwent HDC + HSCT.

### **Lifetime QALY model for comparing treatments**

The observed QALYs were used in a decision model to assess the preferred therapy in a putative 50-year-old RA patient with a life expectancy of 20 years. In this model, conventional treatment was compared with HDC + HSCT by applying a range of hypothetical values of TRM for HDC + HSCT. For conventional therapy, it was assumed that utility remained stable at baseline values. For patients who underwent HDC + HSCT, utility was assumed to follow the observed 5-year utility curve and to remain equal to baseline values for the following 15 years. In accordance with economic evaluations, utilities of future years were discounted at 3%, thus reducing the importance of later years. Using a threshold analysis, we determined the TRM below which HDC + HSCT rendered more QALYs compared to conventional treatment.

### **Statistical analysis**

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows 11.0; SPSS, Chicago, IL). *P* values less than or equal to 0.05 were considered significant. To assess whether there was a significant difference in health status scores up to 9 months after transplantation compared with baseline, one-way analyses of variance (ANOVAs) were performed. Student's *t*-tests were used to explore at which time points after treatment the changes in health status scores from baseline were significant.

## **Results**

### **Clinical results**

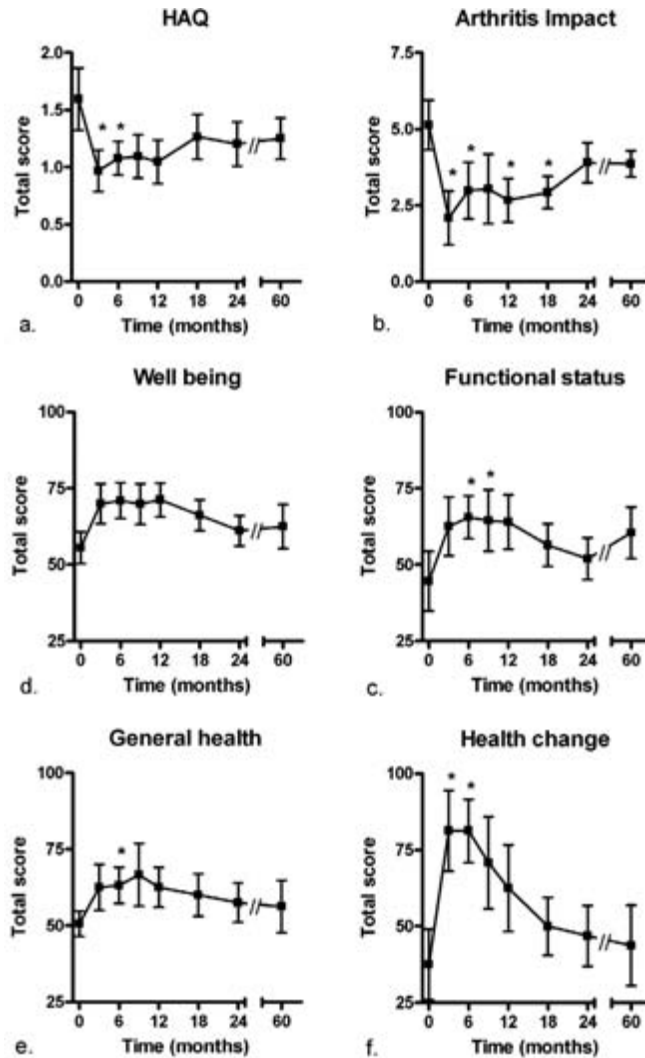
Eight patients with severe, refractory RA were treated with HDC + HSCT. Six months after transplantation, 4 patients showed good improvement, 2 showed moderate improvements, and 2 showed no improvement according to the EULAR response criteria. Two patients fulfilled the criteria of good improvement

both 1 year and 2 years after transplantation, while 5 patients and 4 patients, respectively, showed moderate improvement, and 1 patient and 2 patients, respectively, showed no improvement. All patients had a relapse of disease activity leading to reinstitution of MTX. After 2 years post-transplantation, dosages of MTX ranged from 5 mg/week to 17.5 mg/week in 7 patients, and 1 patient received leflunomide after MTX treatment failed. Three patients also took prednisone at dosages of 7.5-10 mg/day<sup>13</sup>. Of note, all patients showed renewed sensitivity to these DMARDs. Health status maximally improved within 9 months after transplantation, with 4 patients (50%) taking MTX. Nausea, vomiting, and alopecia were observed in all patients, as reported earlier<sup>5</sup>. Grade 3 toxicity (according to the criteria of the World Health Organization<sup>13</sup>) was observed in 1 patient, who had elevated levels of bilirubin, aspartate aminotransferase, and alanine aminotransferase, as well as intolerable diarrhea requiring antibiotic therapy.

Functionality, as measured by the HAQ, showed significant improvements within the first 9 months, with a maximal decrease of mean  $\pm$  SD HAQ scores from  $1.59 \pm 0.27$  before transplantation to  $0.97 \pm 0.18$  at 3 months ( $P=0.02$ ) (Figure 1a). ANOVAs also showed a significant decrease in the HAQ scores ( $P=0.048$ ). Although mean  $\pm$  SD HAQ scores steadily increased up to  $1.25 \pm 0.18$  at 5 years, they did not reach pretreatment values. Even though these values did not differ significantly from those at baseline, the observed changes of  $\geq 0.22$  units are considered clinically significant<sup>14</sup>.

### Improvements in health status

ANOVAs performed for the Arthritis Impact VAS of the AIMS showed a significant decrease over the 9-month period posttransplantation ( $P=0.015$ ), with a maximal decrease in the mean  $\pm$  SD Arthritis Impact scores from  $5.14 \pm 0.81$  to  $2.99 \pm 0.88$  at 3 months ( $P=0.02$ ) (Figure 1b). Three out of 4 summary scales of the generic measure RAND-36 showed significant improvements in mean  $\pm$  SD health status scores compared with baseline scores during the first 9 months after transplantation. Patients' reported scores on functional status increase significantly from  $44.6 \pm 9.73$  to  $65.5 \pm 7.03$  ( $P=0.04$ ). These scores on functional status gradually decreased during follow-up, but they remained above pretreatment values throughout the 5 years of follow-up (Figure 1c).

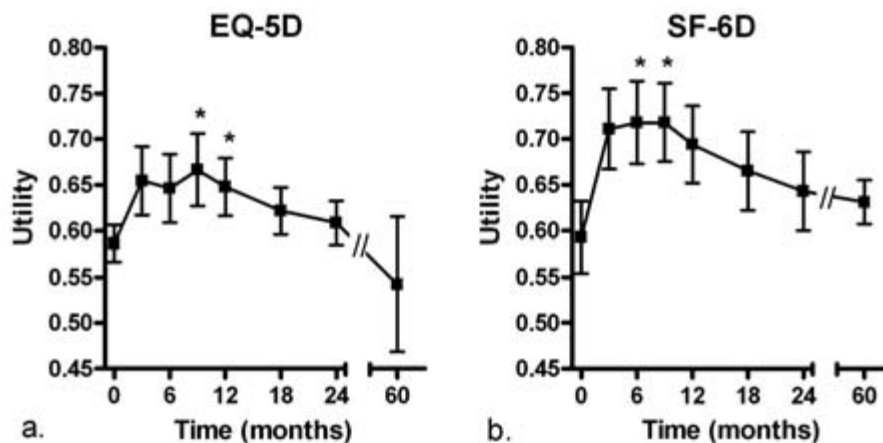


**Figure 1** Health status of patients with severe, refractory rheumatoid arthritis who underwent high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation. **A:** Scores on the Health Assessment Questionnaire (HAQ). Lower scores indicate better health. **B:** Scores on the Arthritis Impact visual analogue scale of the Arthritis Impact Measurement Scales. Lower scores indicate better health. **C-F:** Scores on the four summary scales of the RAND-36 version of the Short Form 36 health survey. Higher scores indicate better health. Values are the mean  $\pm$  SD. \* =  $P \leq 0.05$  versus baseline.

Scores on well-being also improved from  $55.6 \pm 5.19$  to  $70.9 \pm 5.81$  ( $P=0.09$ ) (Figure 1d). General health scores improved significantly from  $50.6 \pm 4.17$  to  $63.1 \pm 5.90$  at 6 months ( $P=0.05$ ) (Figure 1e). Health change scores improved significantly from  $37.5 \pm 11.6$  to  $81.3 \pm 10.3$  at 6 months ( $P=0.01$ ) (Figure 1f). ANOVAs showed significant improvement on the summary scale of health change ( $P=0.015$ ).

### Increased utility scores and QALYs

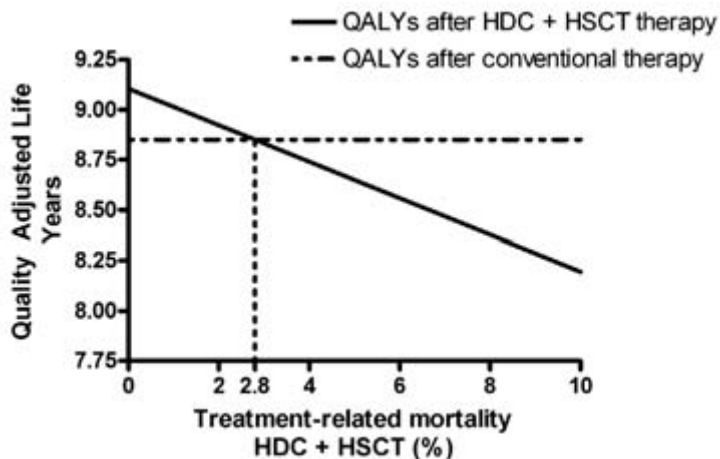
Mean  $\pm$  SD utility scores measured by the EQ-5D questionnaire increased significantly from  $0.51 \pm 0.02$  before transplantation to  $0.67 \pm 0.04$  within 9 months ( $P=0.03$ ) (Figure 2a). During the same period, SF-6D utility scores also increased significantly from  $0.59 \pm 0.11$  to  $0.72 \pm 0.12$  ( $P=0.04$ ) (Figure 2b). The total QALYs, calculated as the AUC from the SF-6D utility score, were 1.4 in the first 2 years post-transplantation and 3.3 after 5 years. Compared with baseline utilities, this increase equals an improvement of 0.28 QALYs.



**Figure 2 A:** Utility scores as measured by the EuroQol (EQ-5D) questionnaire (n = 8 patients). **B:** Utility scores as measured by the Short Form 36 health survey-derived utility index (SF-6D) (n = 8 patients). Values are the mean  $\pm$  SD. \* =  $P \leq 0.05$  versus baseline.

### Lifetime QALY model

Using a threshold analysis, we calculated whether the gained QALYs, as compared with the baseline utilities, could compensate for the TRM of HDC + HSCT. Assuming a life expectancy of 20 years for a 50-year-old patient with severe RA, we found that HDC + HSCT equal conventional therapy in terms of QALYs when the TRM is 2.8 % (Figure 3). For a younger patient with a life expectancy of 30 years, the threshold of TRM would decrease to 2.2%.



**Figure 3** Threshold analysis for treatment-related mortality (TRM) of high-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (HSCT) in a putative 50-year-old rheumatoid arthritis patient with a 20-year life expectancy. The analysis determines the threshold TRM above which HDC+HSCT results in superior quality-adjusted life years (QALYs) compared with continued conventional therapy, based on the assumption that conventional therapy results in stable QALYs over the 20-year period. A TRM less than 2.8% favors HDC+HSCT as the preferred treatment when compared to continued conventional therapy.

### Discussion

The aim of this study was to analyze the health status of patients with previously refractory RA patients during 5 years following HDC + HSCT. Our study demonstrates significant improvement of health status, notably in the first 9 months posttransplantation. We also showed that utility scores improved for patients who underwent HDC + HSCT, and that the QALYs gained for RA

patients treated with HDC + HSCT outweighed those for RA patients treated with conventional therapy when TRM was <2.8%.

The European Group for Blood and Marrow Transplantation reported that TRM after HDC + HSCT occurred in 1 of 76 RA patients (1.3%)<sup>4</sup>. Therefore, our study indicates that in a hypothetical 50-year-old RA patient with a life expectancy of 20 years, HDC + HSCT results in superior health status compared with conventional therapy. Of note, it should be taken into account that the threshold for TRM is higher in older patients with shorter life expectancy because TRM leads to a smaller QALY loss.

To our knowledge, this is the first comprehensive study on the long-term follow-up of the health status of patients with severe, refractory RA. The health status of these patients improved after HDC + HSCT mainly in the first 9 months posttransplantation and lasted for as long as 2 years. HAQ scores improved by  $\geq 0.22$  units, considered clinically significant, during the complete follow-up period. Furthermore, utilities increased as measured by 2 different generic measures, the SF-6D and the EQ-5D questionnaire. Despite conceptual differences, both utility measures yielded very similar results. In addition, using the AIMS, we also found significant improvement in the impact of arthritis on the health status of patients who underwent HDC + HSCT. Interestingly, there were 2 nonresponders within this group of patients. HDC + HSCT had more pronounced effects on health status and utility scores in the group of 6 responders (data not shown).

The remarkable improvement in health status after HDC + HSCT was mainly achieved during the first 9 months posttransplantation. Because conventional DMARD therapy was reinstituted in 50% of the patients at 9 months, it can be assumed that the improved health status of RA patients is related directly to HDC + HSCT. Indirectly, HDC + HSCT caused renewed sensitivity to DMARD therapy in all patients, which accounted for the prolongation of health status improvement up to 2 or even up to 5 years.

A limitation of our study is that we could not correct for a placebo effect, since HDC + HSCT was tested as an investigational treatment in a nonrandomized pilot study. Other limitations were the small number of patients enrolled in this

study and the lack of adequate data on health status in a control group of patients with severe RA. We postulated that health status and utility scores were, at best, stable at baseline values for patients with severe RA treated with conventional therapy<sup>15</sup>.

We estimated an improvement of 0.28 QALYs for patients with severe RA treated with HDC + HSCT. Wong *et al.*<sup>2</sup> showed a comparable improvement of 0.33 QALYs over a 1-year period in RA patients treated with a TNF-blocking agent combined with MTX compared with MTX alone, based on data from the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy and from the Arthritis, Rheumatism, and Aging Medical Information System<sup>1</sup>. However, those patients had less severe disease activity than our patients who underwent HDC + HSCT, and the safety and tolerability of continued TNF-blocking therapy still has to be confirmed<sup>2</sup>.

From our data, it can be concluded that HDC + HSCT improves the health status of patients with severe RA. Nevertheless, the treatment is not curative, as reflected in the return of health status to near-baseline levels after 2-5 years post-transplantation. Therefore, new experimental therapies should aim at prolonging the initial benefit of high-dose immunosuppression without significantly increasing TRM.

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