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BRIEF REPORT

Long-Term Outcome of a Randomized Clinical Trial Comparing Methotrexate to Cyclophosphamide for Remission Induction in Early Systemic Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Objective. **The NORAM (Nonrenal Wegener's Granulomatosis Treated Alternatively with Methotrexate [MTX]) trial demonstrated that MTX can replace cyclophosphamide (CYC) as remission-inducing treatment for patients with newly diagnosed early systemic antineutrophil cytoplasmic antibody–associated vasculitis. Duration of relapse-free survival was longer among CYC-treated patients than among MTX-treated patients during short-term followup. The aim of the present study was to describe the long-term outcome in patients enrolled in the randomized clinical trial.**

Methods. **Outcome questionnaires were sent to investigators who had recruited patients for the NORAM trial. Patients treated with MTX for induction of remission (n = 49) were compared to CYC-treated patients (n = 46) with respect to immunosuppressive therapy during followup, relapse-free survival, mortality, and occurrence of other clinical events.**

Results. **The median duration of followup was 6 years (range 0.1–10.8 years). One patient developed end-stage renal disease, and 11 died. The number of patients affected by serious infection, malignancy, or severe organ failure did not differ between treatment groups, and no difference in survival rate was observed. The duration of corticosteroid therapy was longer in the MTX group during the 18 months of the trial ($P = 0.005$). During subsequent followup, patients who were in the MTX group in the NORAM trial received corticosteroids, CYC, and other immunosuppressive agents (azathioprine, MTX, and/or mycophenolate mofetil) for longer periods than those who were in the CYC group ($P = 0.004$, $P = 0.037$, and $P = 0.031$, respectively). The cumulative relapse-free survival tended to be lower in the MTX group ($P = 0.056$).**

Conclusion. **In the NORAM cohort, no difference in occurrence of major adverse events was observed between treatment groups during long-term followup. However, first-line treatment with MTX was associated with less effective disease control than CYC-based induction therapy.**

Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) are vasculitic disorders associated with the presence of circulating antineutrophil cytoplasmic antibodies (ANCAs). The introduction of cyclophosphamide (CYC) to induce remission greatly improved the prognosis of patients with ANCA-associated vasculitides (AAVs). However, CYC-based treatment regimens for AAV has been associated with a pronounced risk of treatment-related comorbidity, especially when CYC therapy is prolonged (1).

Clinical trials conducted by the European Vasculitis Study Group have explored the value of alternative therapeutic approaches to AAV, including approaches involving reduced exposure to CYC (2–4). The NORAM (Nonrenal Wegener's Granulomatosis Treated Alterna-

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tively with Methotrexate [MTX]) trial was a randomized trial designed to clarify whether MTX can replace CYC as first-line therapy for AAV patients without disease manifestations threatening vital organ function (early systemic AAV) (2). Patients enrolled in the trial were randomized at diagnosis to receive corticosteroids in combination with weekly oral MTX or daily oral CYC. For patients whose disease was in complete remission, all therapy was discontinued after 12 months, and the patients were subsequently followed up for a further 6 months. The remission rate in the MTX group was not inferior to that in the CYC group, confirming that treatment with MTX and corticosteroids constitutes a therapeutic option for AAV patients with nonsevere clinical disease features (5). The median time from remission to relapse was longer among CYC-treated patients than among MTX-treated patients during the 18-month trial. To further investigate the efficacy of MTX-based induction therapy in early systemic AAV, we assessed mortality, treatment, and relapse-free survival during long-term followup of patients enrolled in the NORAM study.

PATIENTS AND METHODS

Patients. Patients were recruited for the trial between 1995 and 2000. The study design was previously described (2). Briefly, patients with newly diagnosed GPA or MPA presenting with manifestations of vasculitis in ≥1 organ system in combination with constitutional symptoms were considered eligible for the study. Additional inclusion criteria encompassed the following: erythrocyte sedimentation rate >45 mm/hour and/or C-reactive protein level >2 times the upper limit of normal, or ANCA positivity, or a nonrenal biopsy showing alterations compatible with GPA or MPA. Exclusion criteria were as follows: organ- or life-threatening manifestations, serum creatinine level >150 μmoles/liter, urinary red blood cell casts or urinary protein excretion >1.0 gm/day, cutaneous vasculitis only, coexistence of another autoimmune disorder, malignancy, active hepatitis B virus infection, human immunodeficiency virus infection, and age <18 years or >75 years.

Patients in the CYC group (n = 46) received oral CYC 2 mg/kg/day (maximum 150 mg/day) until remission, for a minimum of 3 months and a maximum of 6 months. The CYC dosage was reduced by 25 mg/day in patients >60 years of age. After remission was achieved, the CYC dosage was reduced to 1.5 mg/kg/day until month 10, when treatment was tapered and discontinued by month 12. Patients in the MTX group (n = 49) received oral MTX at a maximum dosage of 25 mg/week (starting at 15 mg/week with dosage escalation over 3 months) until month 10, when the treatment was tapered and discontinued by month 12. Patients in both treatment groups received oral prednisolone at an initial dosage of 1 mg/kg/day. The prednisolone dosage was tapered to 15 mg/day by month 3, to 7.5 mg/day by month 6, and was discontinued by month 12. From month 12 to month 18, patients whose disease was in remission received no immunosuppressive therapy. After conclusion of the trial (from month 19 and onward), patients were treated according to local practice.

Treatment and outcome during long-term followup. In 2004, outcome questionnaires were sent to investigators who had recruited patients to the trial (see Appendix A). Replies were collected between 2004 and 2007. In some cases, the doctors who completed the questionnaires differed from those who recruited patients to the trial. Local investigators were asked to provide information on the vital status of patients included in the trial, the number of disease relapses after termination of the trial, comorbidity, and causes of death. They were also asked to determine whether their patients had been receiving immunosuppressive agents, including CYC, azathioprine, MTX, mycophenolate mofetil, and corticosteroids during different followup periods (months 19–24, months 25–36, months 37–48, and months 49–60). Information on treatment and clinical events within the trial period (months 1–18) was obtained from the original study files.

Between month 1 and month 18, the exact duration of treatment with CYC and corticosteroids could be calculated based on available data. The duration of drug exposure between months 19 and 60 could not be precisely determined due to the design of the long-term outcome questionnaire. As an approximation, we therefore defined drug exposure during months 19–24 as being equivalent to a treatment duration of 6 months and drug exposure during months 25–36, 37–48, and 49–60 as being equivalent to a treatment duration of 12 months per interval. In these analyses, patients were considered as having been treated with CYC if both CYC and a disease-modifying antirheumatic drug (DMARD) had been administered during a given time interval.

Statistical analysis. Analyses were performed on an intent-to-treat basis. We used life tables and the Kaplan-Meier method for determination of cumulative patient survival and cumulative relapse-free survival. The log rank test was used for comparison of Kaplan-Meier curves. The analyses of relapse-free survival were terminated at 5 years due to a low number of remaining cases beyond this time point. The Mann-Whitney U test was used for comparison of continuous data, while the chi-square test or Fisher's exact test was used for comparison of categorical data. All analyses were performed using IBM SPSS Statistics version 19.0.

RESULTS

The median age of the 95 patients was 53 years (range 18–78 years) at the time of enrollment in the NORAM trial. Eighty-nine patients (94%) had GPA, and 6 (6%) had MPA. The study included 51 women (54%). Proteinase 3 (PR3) ANCA was found in 70 patients (74%), while myeloperoxidase ANCA was found in 12 (13%).

During the 18-month trial, 4 patients died, 4 were withdrawn from the trial, and 3 were lost to followup. Questionnaires regarding long-term outcome were returned for 70 of the 84 patients who completed the trial

and for 2 of those who were withdrawn from the study before completion. Thus, a total of 72 patients were followed up for >18 months. Patients lost to followup before month 19 did not differ from those followed up for longer periods with respect to baseline characteristics or number of relapses during the trial phase (data not shown). There were no differences between the 2 treatment groups in the numbers of patients lost to followup before month 19.

Table 1 summarizes clinical outcome data stratified according to treatment group. The median duration of followup was 6.0 years (range 0.1–10.8 years), with no differences between groups. One patient (MTX group) with renal involvement developed end-stage renal disease (ESRD) at 3 years. Eight patients developed malignant disease (in the CYC group, 1 each of nonmelanoma skin cancer, rectal cancer, and colon cancer, and in the MTX group, 1 each of pancreatic cancer, prostate cancer, breast cancer, and myelodysplastic syndrome, and 1 case of 2 malignancies [breast and cervical cancers]). Followup data on serious infections requiring hospitalization were available for 91 patients. Among these, 7 experienced severe infectious complications within the trial period, while 11 were hospitalized due to infection after conclusion of the trial. The number of patients affected by ESRD, cancer, or serious infections did not differ between groups. Severe forms of disease- or treatment-related nonrenal organ failure were reported for 3 patients in each treatment group (in the CYC group, vision loss in 2 patients, and respiratory failure in 1, and in the MTX group, respiratory failure, avascular necrosis, and infertility in 1 patient each; data available for 90 patients). Five patients in each group experienced bone fracture during followup (data available for 93 patients).

The duration of corticosteroid therapy was longer in the MTX group than in the CYC group within the trial period ($P = 0.005$) (Table 1). During subsequent followup, patients in the MTX group were exposed to corticosteroids, CYC, and DMARDs for longer periods of time than patients in the CYC group ($P = 0.004$, $P = 0.037$, and $P = 0.031$, respectively).

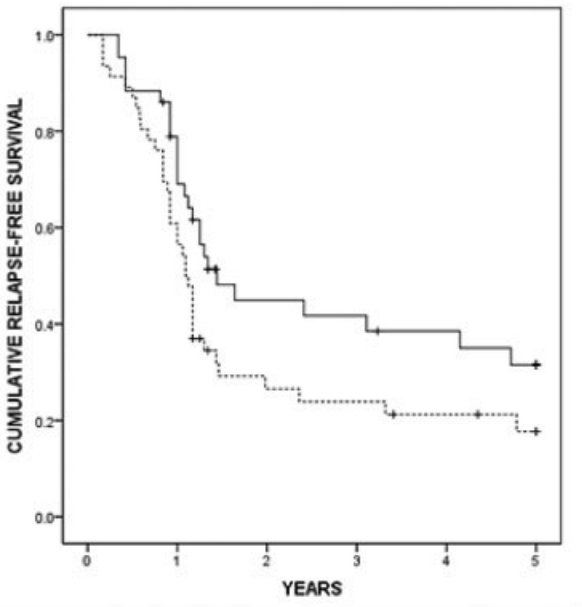
Remission was achieved in 89 patients during the trial, 2 had persistent disease activity, 3 were lost to followup or were withdrawn from the trial before remission was achieved, and 1 died after 2.5 months of induction therapy with CYC. The cumulative relapse-free survival from time of first remission was 69%, 32%, and 24% after 1, 3, and 5 years of followup, respectively. As shown in Figure 1, the cumulative relapse-free survival tended to be higher in the CYC group than in the MTX group ($P = 0.056$ by log rank test). Three patients experienced a first relapse >5 years after remission. In a supplementary analysis, we compared the relapse-free survival between treatment groups without censoring at 5 years. In this analysis, we observed a comparable difference in relapse-free survival between treatment groups ($P = 0.059$ by log rank test). When analyzed from time of trial entry, the cumulative relapse-free survival in

Table 1. Clinical characteristics of patients in the NORAM cohort during long-term followup*

	CYC group (n = 46)	MTX group (n = 49)	*P*
Duration of followup, median (IQR) years	6.0 (1.6–7.7)	6.0 (1.6–7.3)	0.8
Deaths, no. (%)	5 (10.9)	6 (12.2)	1.0
Patients with malignancies, no. (%)	3 (6.5)	5 (10.2)	0.7
Patients with serious infections, no. (%)†	8 (18.2)	10 (21.3)	0.7
Patients with end-stage renal disease, no. (%)	0 (0)	1 (2.0)	1.0
Cumulative duration of therapy within trial (months 1–18), median (IQR) months			
CYC	12 (12–12)	0 (0–0)	–
Corticosteroids	12 (12–15)	15 (12–18)	0.005
Cumulative duration of therapy after trial (months 19–60), median (IQR) months			
CYC	0 (0–6)	6 (0–12)	0.037
DMARDs	12 (0–24)	18 (12–36)	0.031
Corticosteroids	18 (0–36)	36 (18–42)	0.004

* Followup began at the time of NORAM (Nonrenal Wegener's Granulomatosis Treated Alternatively with Methotrexate [MTX]) trial entry and continued until the time of last recorded hospital visit, withdrawal from the trial, death, or loss to followup. Disease-modifying antirheumatic drugs (DMARDs) included azathioprine, MTX, and/or mycophenolate mofetil. CYC = cyclophosphamide; IQR = interquartile range.

† Four patients were excluded from this analysis (2 from each treatment group) due to missing data.



CYC	43	32	14	13	11	9
MTX	46	28	10	9	7	5

Figure 1. Cumulative relapse-free survival from time of first remission in the cyclophosphamide (CYC) group (solid line) and in the methotrexate (MTX) group (dotted line) in the Nonrenal Wegener's Granulomatosis Treated Alternatively with MTX cohort. Only patients in whom remission was achieved during the 18-month clinical trial were included in the analysis (n = 89). Numbers of patients at risk by year of followup are indicated below the graph. Cumulative relapse-free survival tended to be higher in the CYC group than in the MTX group ($P = 0.056$ by log rank test).

the cohort after 1, 2, 3, 4, and 5 years of followup was 83%, 37%, 32%, 29%, and 26%, respectively.

Eleven patients died during followup, and the cumulative survival after 1, 3, and 5 years was 98%, 93%, and 89%, respectively. No differences in cumulative survival were found between groups ($P = 0.88$ by log rank test). Fatalities were determined to be due to vasculitis (2 patients), infection (3 patients), cancer (3 patients), and pulmonary fibrosis (1 patient). In 2 cases, the direct cause of death could not be determined.

DISCUSSION

The NORAM study demonstrated that MTX had similar efficacy to CYC when combined with corticosteroids for induction of remission, but it was associated with a higher early relapse rate in patients with early systemic AAV. The short duration of the trial prevented an evaluation of the long-term consequences of substituting MTX for CYC. In the current study, we assessed the outcome in the cohort after a median of 6 years.

The observed 5-year survival rate of 89% is comparable to the survival described in some AAV studies (6,7) but higher than reported in other investigations (8–10). The relatively low mortality observed in our cohort can be explained by the eligibility criteria of the NORAM protocol, which prevented inclusion of patients with life-threatening disease manifestations, including severe glomerulonephritis.

The cumulative relapse-free survival after 5 years was only 24%. Several factors may contribute to the low rate of relapse-free survival. PR3 ANCA positivity and ear, nose, and throat involvement are risk factors for relapsing disease (8,11–13), and these disease features were common in our cohort. Moreover, patients with GPA have a higher relapse risk than those with MPA (3,8,13), and 94% of our patients had GPA. Finally, the NORAM protocol required cessation of immunosuppression after 12 months of treatment, and the absence of remission-maintenance therapy after 1 year probably had a negative effect on the relapse-free survival, which decreased dramatically during the second year of followup. Relapse-free survival declined considerably in both treatment groups during this time interval, demonstrating that patients with early systemic AAV have a high risk of relapse regardless of the induction regimen. Though the optimal therapeutic approach to early systemic AAV cannot be deduced from the NORAM data, this observation suggests that, similar to patients with generalized vasculitis (3), AAV patients with early systemic disease require immunosuppressive maintenance therapy after induction of remission. The need for maintenance therapy is also indicated by the prolonged median duration of DMARD and corticosteroid use in both treatment groups during months 19–60.

Only 1 of 95 patients (1%) in the cohort developed ESRD during the followup period. A comparable observation was made by Villa-Forte et al in their study of 25 patients with GPA presenting with mild to moderate disease (patients without severe renal disease or other critical organ manifestations). They found that only 1 patient experienced progressive renal failure during long-term followup (7). These findings, taken together with ours, show that patients with early systemic AAV have a better renal prognosis than other AAV patients despite the high risk of a relapsing disease course.

The number of serious infections did not differ

between treatment groups, indicating that the risk of infection was not driven by CYC exposure. We did not observe a higher occurrence of malignancies in the CYC group than in the MTX group. However, CYC-induced cancers, such as bladder carcinomas and myeloid leukemias, typically develop with a latency of >5 years, and it is not uncommon for treatment-related bladder cancers to occur >10 years after CYC therapy (14). A longer duration of followup is therefore needed to fully assess the cancer risk in the cohort.

Although the NORAM trial demonstrated noninferiority of MTX compared to CYC for induction of remission in early systemic AAV, patients in the MTX group received higher cumulative doses of corticosteroids and experienced shorter relapse-free survival than patients in the CYC group during the 18-month trial. The limitations of MTX-based first-line therapy according to the NORAM protocol are further illustrated by the present analyses. The cumulative relapse-free survival tended to be lower in the MTX group than in the CYC group after prolonged followup ($P = 0.056$), mainly due to a high occurrence of relapses in the MTX group during the second year of study. Furthermore, the average duration of treatment with corticosteroids, CYC, and DMARDs was longer in the MTX group than in the CYC group during months 19–60. These observations indicate that patients initially treated with MTX experienced disease remissions that were less stable than the remissions experienced by patients treated with CYC. Thus, our observations add to a range of clinical data demonstrating that the intensity of first-line immunosuppressive treatment is inversely related to the risk of relapsing disease in AAV (9,12,15). It could be speculated that the threshold for initiating therapy with corticosteroids and CYC during followup was influenced by the treating physicians' perception of MTX as a weaker remission-inducing agent than CYC, but the lower cumulative relapse-free survival rate and the longer average duration of DMARD therapy in the MTX group provide evidence against this hypothesis.

The median duration of corticosteroid therapy from months 19 to 60 was 3 years in the MTX group and only 1.5 years in the CYC group. Since current induction therapy for early systemic AAV typically involves the use of DMARDs or administration of much lower cumulative CYC doses than dictated by the NORAM protocol, our findings underscore that patients presenting with this subtype of AAV must be monitored closely for development of relapse after remission induction and that corticosteroid-sparing treatment strategies should be considered for those with a chronic relapsing disease course.

The current study has several limitations. We did not have access to data on the severity of relapses occurring after termination of the NORAM trial or to detailed information on treatment- and disease-induced organ damage during long-term followup (e.g., osteoporosis, cataract, obesity, infertility, minor infections), and this prevented a more detailed analysis of clinical outcomes. Information regarding cumulative drug doses was not available, and we were unable to assess the relationship between relapse risk and cumulative medication exposures. Finally, the prolonged administration of CYC and the early discontinuation of immunosuppressive therapy during the 18-month trial period conflict with current treatment recommendations. Therefore, the present investigation can only be used to evaluate the efficacy of MTX-based first-line therapy as per the NORAM protocol.

In summary, our study provides data on long-term outcome in AAV patients recruited for the NORAM trial. Patients who received MTX for remission induction were treated with corticosteroids, CYC, and DMARDs for significantly longer periods of time after conclusion of the trial than patients initially treated with CYC, and cumulative relapse-free survival tended to be lower in the MTX group. Despite the methodologic limitations mentioned above, these findings demonstrate that first-line treatment with MTX was associated with less effective long-term disease control than CYC-based therapy in the NORAM cohort.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Jayne had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Westman, Rasmussen, de Groot, Jayne.
Acquisition of data. Faurschou, Westman, Rasmussen, de Groot, Flossmann, Jayne.
Analysis and interpretation of data. Faurschou, Rasmussen, Höglund, Jayne.

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APPENDIX A: NORAM TRIAL PARTICIPATING PHYSICIANS AND WRITING COMMITTEE MEMBERS

The following physicians participated in the NORAM trial: D. Blockmans (Universitaire Ziekenhuis, Leuven, Belgium), A. Wiik (Statens Serum Institut, Copenhagen, Denmark), P. Lesavre (Hôpital Necker, Paris, France), P. Bataille (Centre Hospitalier General, Boulogne sur Mer, France), L. Guillevin (Hôpital Avicenne, Bobigny, France), P. Vanhille (Centre Hospitalier, Valenciennes, France), O. Hergesell, K. Andrassy (Heidelberg University Hospital, Heidelberg, Germany), E. Reinhold-Keller (Rheumaklinik, Bad Bramstedt, Germany), C. Specker, M. Schneider (Heinrich-Heine University, Dusseldorf, Germany), M. Haubitz (Medical School, Hannover, Germany), F. van der Woude (Klinikum, Mannheim, Germany), H. Rupprecht, S. Weidner (Klinikum, Nuremberg, Germany), A. Natusch (Klinikum Buch, Berlin, Germany), M. Abuzakouk (St. James's Hospital, Dublin, Ireland), A. Sinico (Ospedale San Carlo, Borromeo, Italy), G. Poisetti (Ospedale Civile, Piacenzia, Italy), J. Dadoniene, (University of Vilnius, Vilnius, Lithuania), E.C. Hagen (University Eemland Hospital, Amersfoort, The Netherlands), C. G. M. Kallenberg, C. M. Stegeman (Groningen University Hospital, Groningen, The Netherlands), C. Verburgh (Leiden University Medical Centre, Leiden, The Netherlands), E. Mirapeix (Hospital Clinic I Provincial, Barcelona, Spain), M. Heimburger (Huddinge University Hospital, Huddinge, Sweden), C. Stahl-Hallengren, M. Segelmark (University Hospital of Lund, Lund, Sweden), E. Theander (University Hospital of Malmo, Malmo, Sweden), Z. Heigl, I. Lundberg, E. Svenungsson (Karolinska Sjukhuset, Stockholm, Sweden), J. Gibson (Windygates Hospital, Fife, UK), D. Adu, C. Savage (Queen Elizabeth II Hospital, Birmingham, UK), P. Kieley (St. George's Hospital, London, UK), G. Gaskin, C. Pusey (Hammersmith Hospital London, London, UK).

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