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Updated Experience with Inolimomab as Treatment for Corticosteroid-Refractory Acute Graft-versus-Host Disease

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A B S T R A C T

Refractory acute graft-versus-host disease (aGVHD) remains an important cause of mortality after allogeneic stem cell transplantation. No standard therapy exists once steroids fail to obtain a good response. In 2006, our group published a series of patients who received inolimomab, an anti–interleukin-2 receptor monoclonal antibody, as salvage therapy with initial encouraging results. In this update, we analyzed a larger group of patients with prolonged follow-up. Ninety-two consecutive patients were treated with inolimomab at our center between April 1999 and December 2011. Overall response rate was 42% (complete response in 14%) on day +30. Predictors of failure to respond in the multivariate analysis were overall aGVHD grade IV, instauration of inolimomab before day 15 of aGVHD diagnosis, and severe lymphopenia. Patients without gastrointestinal involvement appeared to do better, with a 70% response rate compared with 39% in patients with gastrointestinal involvement ($P = .06$). However, the 2-year overall survival rate was of 18% for the entire cohort (95% confidence interval, 10% to 26%) and 33% for day 30 responders (95% confidence interval, 25% to 40%) and Acute GVHD was the main cause of death (49%) followed by opportunistic infections (27%). Results of this update show that although inolimomab is a well-tolerated drug with a moderate number of short-term responses, it is associated with long-term survival in only one-third of responding patients. These data highlight the need to investigate new rescue treatments with sustained effect and the importance of reporting long-term outcomes in GVHD studies.

INTRODUCTION

Acute graft-versus-host disease (aGVHD) is the most important cause of non-relapse mortality after allogeneic stem cell transplantation. Its incidence varies between 30% and 80% depending on various risk factors (eg, recipient age, gender disparity, cytomegalovirus serostatus, disease status, stem cell source, human leukocyte antigen mismatch, etc.), and its initial therapy consists of systemic corticosteroids (2 mg/kg daily prednisone or equivalent dose of other steroids) [1-3]. Refractoriness to steroids, which occurs in approximately 50% of patients, is associated with a poor prognosis (approximately 5% to 30% of long-term survivors) [3]. Although multiple second-line therapies (antithymocyte globulin, mycophenolate mofetil, sirolimus, photopheresis, etc.) have been used, often with initial encouraging results, none has been established as a good option, and there is no defined standard salvage therapy [3,4]. The development of new strategies for effective intervention before the development of steroid-refractory disease is also under study. A multicenter, randomized, double-blind, phase III trial evaluating the addition of mycophenolate mofetil versus placebo in addition to systemic corticosteroids as initial therapy for aGVHD was closed early for accrual in November 2011 due to lack of benefit [5,6].

New, recently published recommendations [7-9] call for the establishment of a common formal structure in aGVHD studies. Clear definition of inclusion and response criteria (avoiding best response as endpoint), 28-day evaluation of efficacy, considering as failure the use of other salvage treatment(s), and including at least a 6-month overall survival (OS) rate are some of the most important recommendations.

New advances in the understanding of aGVHD immune pathophysiology emphasize the important role that inflammatory interleukins have in the activation and proliferation of effector T cells, making them an interesting target for monoclonal antibodies [10-12]. In June 1999, we began to use inolimomab, a monoclonal antibody directed against the interleukin-2 receptor, for refractory aGVHD, and since 2006 this has been our standard salvage therapy for steroid-refractory aGVHD [13], based on preliminary encouraging results (58% overall responses, 38% complete responses [CRs], and 59% 1-year survival in responding patients).

In this article, we update our results in a larger group of patients with prolonged follow-up. We made an effort to improve the quality of the study by following the recent recommendations [7] considered important in reporting aGVHD studies.

METHODS

This single-center, retrospective study analyzed the outcomes of 92 consecutive adult patients who received inolimomab as salvage treatment for steroid-refractory aGVHD between April 1999 and December 2011. The sole treatment criterion was presence of steroid-refractory grades II to IV aGVHD, including both classical and late-onset forms. Three patients diagnosed with an overlap syndrome who presented predominantly aGVHD

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Table 1
Patient Characteristics

Characteristics	Value n (%)
Median age, yr (range)	50 (17-68)
Gender male	65 (71)
Sex mismatch: female donor to male recipient	25 (27)
Underlying disease	
Acute leukemia	29 (32)
MDS and MPS	29 (32)
Chronic lymphoproliferative diseases	25 (27)
Others	9 (10)
Advanced disease status at HSCT	59 (64)
Recipient and donor CMV negative	7 (8)
Stem cell source	
Peripheral blood	77 (84)
Bone marrow	10 (11)
Cord blood	5 (5.4)
Donor type	
HLA identical sibling	52 (56)
Alternative	40 (44)
EBMT risk index	
Low risk (score 0-1)	9 (10)
Intermediate risk (score 2-3)	38 (41)
High (score 4-6)	45 (49)
Conditioning regimen	
Reduced intensity (fludarabine plus melphalan or busulphan)	65 (71)
High-dose myeloablative	28 (30)
Alemtuzumab or ATG pretransplantation	16 (17)
GVHD prophylaxis	
CsA-based immunosupression	85 (92)
Tacrolimus plus sirolimus	7 (8)
Inolimomab as first-line salvage therapy	46 (50)
NR to prior salvage therapies	46 (50)
MMF	22 (24)
ATG	20 (22)
CsA	3 (3)
Median time from allo-SCT to aGVHD onset, d (range)	34 (5-170)
Median time from onset of aGVHD to start of inolimomab, d (range)	16 (2-204)
Overall aGVHD grade at start of inolimomab	
II	6 (6.5)
III	48 (52)
IV	38 (41)
Organs involved by aGVHD at the start of inolimomab	
GI tract	82 (90)
Liver	64 (70)
Skin	79 (86)
Platelets at the start of inolimomab, $\times 10^9$/L, median (range)	40 (2-264)
Lymphocyte count at the start of inolimomab, $\times 10^9$/L, median (range)	0.33 (0-2.5)
Albumin at the start of inolimomab, g/L, median (range)	26 (13-42)

MDS indicates myelodysplastic syndrome; MPS, myeloproliferative syndrome; HSCT, hematopoietic stem cell transplantation; CMV, cytomegalovirus; EBMT, European Group for Blood and Marrow Transplantation; CsA, cyclosporine A; MMF, mycophenolate mofetil; ATG, antithymocyte globulin. Advanced disease status was considered in patients with acute leukaemia in at least second CR, myeloproliferative disease in at least second chronic phase, accelerate or blast phase, Hodgkin disease in at least third complete remission or with PR, follicular lymphoma in at least third CR, large B cell lymphoma or multiple myeloma in at least second CR or PR, and solid tumors. Patients with persistent disease at transplantation (except for myeloma) were also considered as advanced disease status.

manifestations were also included. Diagnosis of aGVHD was based on clinical findings and confirmed with histological evaluation of affected organ(s). Overall grading followed the Przepiorka standard criteria [14]. Failure of corticosteroids was defined by overall aGVHD grade progression within 3 days of treatment or absence of response by day 5. No patients were excluded because of active infection, progressive disease, poor performance status, or any other cause. All patients gave their informed consent, and the drug was administered as compassionate use after approval by our institutional and national health authorities. During the study, 3 patients were considered for a clinical trial using mesenchymal cells after failure of inolimomab therapy and thus were not excluded from the analysis.

Inolimomab was administered intravenously at a dose of 11 mg/d for 3 days, 5.5 mg/d for 7 days, and 5.5 mg every other day for 5 doses (21 days per course). Sixty-five patients (71%) received 1 course of inolimomab, 25 patients (27%) received 2 courses, and 2 patients received 3 courses due to absence of response or relapse after responding to a first course of the drug. In addition to steroids, other prior immunosuppressors were not discontinued at the start of inolimomab, with the exception of patients who were on antithymocyte globulin.

Staging of target organs and the overall grade of aGVHD was done in detail at baseline and on days +7, +15, +30, and +60 of the start of inolimomab. CR was defined as the sustained disappearance of all GVHD clinical and laboratory features, whereas partial response (PR) was an overall improvement of at least 1 grade without progression in any organ. The overall response rate (ORR) includes CR plus PR rates. Those patients who showed improvement in 1 organ but progressed in another were considered to have progression of aGVHD. No response included stable, progressive aGVHD and patients who started another drug as salvage therapy.

Recent studies [8,9] have shown that the day 28 response is the strongest predictor of non-relapse mortality (NRM) after starting therapy for aGVHD. For this reason, we selected "day +30 response" as the primary early endpoint (detailed in Statistical Analysis, below). All patients received the treatment as inpatients in HEPA-filtered-air rooms. Supportive measures were considered of primary importance in these patients and included in all instances antiviral, antifungal, and cotrimoxazole prophylaxis. Serial blood monitoring of galactomanan, cytomegalovirus infection, and Epstein-Barr virus infection was done 1-3 times a week, as described elsewhere [15].

Statistical Analysis

Cross-tabs and the Student's *t* test were used to identify baseline characteristics associated with the day +30 response to inolimomab. Response and survival endpoints were calculated using the starting date of inolimomab therapy. Factors associated with ORR on day +30 in univariate analysis ($P < .10$) were then entered into a multivariate Cox regression analysis. *P* values <.05 were considered statistically significant, and hazard ratios and 95% confidence intervals (CIs) were calculated. Survival was estimated by the Kaplan-Meier method, and comparisons of actuarial curves were made with the log-rank test. Finally, to evaluate the impact of the day +30 response on survival, we performed a landmark analysis including only those patients who were alive on day +30 (n = 58).

RESULTS

Patients and GVHD Characteristics

Characteristics of the 92 patients treated are detailed in Table 1. All patients were diagnosed with hematological malignancies, and 90% had an intermediate or high European Group for Blood and Marrow Transplantation risk score before allogeneic stem cell transplantation. Donors were human leukocyte antigen–identical siblings in 52 cases (57%).

Several GVHD prophylaxis regimens were used and, in 78% of cases, were cyclosporine-based combinations (plus methotrexate or mycophenolate mofetil). The median follow-up for survivors was 60 months (range, 6-145). aGVHD occurred at a median of 34 days after transplantation (range, 5-170 days), and 94% of patients developed grade III or IV aGVHD. Involved organs were the gastrointestinal (GI) tract in 82 cases (90%), the liver in 64 (70%), and the skin in 79 (86%). Inolimomab was initiated at a median of 17 days (range, 2-204 days) after the onset of aGVHD. Forty-six patients (50%) received inolimomab as first-line salvage therapy, whereas another 46 patients received this treatment after failure of prior therapy for steroid-refractory aGVHD (see Table 1 for details).

Toxicity and Infections

Inolimomab was well tolerated, without infusion-related reactions. Two patients developed probable drug-related side effects. One of them developed a rapid increase of liver transaminases (without prior hepatic GVHD or use of parenteral nutrition), and inolimomab was discontinued after 10 days of therapy. The other patient developed a mild cutaneous rash that required only symptomatic therapy.

Complete data regarding infectious complications were available for 84 patients (91.3%). Seventy-two developed at least 1 infectious episode during the follow-up period. Cytomegalovirus reactivation was detected in 49 patients (15 with cytomegalovirus disease) at a median time of 7 days (range, +1 - +103 days) from the start of the therapy. Twenty patients (22%) developed an invasive fungal infection (14 cases of invasive aspergillosis and 4 cases of candidemia). Fifty-three patients developed at least 1 bacterial infection, being staphylococcal bacteremia the most common of these infections (n = 26 patients).

Response

The ORR on days +15, +30, and +60 of therapy was 36% (CR 2%), 42% (CR 14%), and 46% (CR 26%), respectively. Patients who received inolimomab as first-line salvage therapy presented an ORR of 39% (CR 0%), 39% (CR 13%), and 50% (CR 26%) on days +15, +30 and +60, respectively, days +15, +30, and +60. Patients without GI involvement (n = 10) responded better, with a 70% response rate compared with a 39% response rate in patients with GI involvement (n = 82; $P = .06$).

Predictors of day +30 response are shown in Table 2. In multivariate analysis, grades II to III overall aGVHD (hazard ratio, 1.8; 95% CI, 1.1 to 3.2; $P = .03$), no severe lymphocytopenia (hazard ratio, 1.9; 95% CI, 1.1-3.3; $P = .02$), and onset of inolimomab later than 15 days after aGVHD diagnosis (hazard ratio, 1.9; 95% CI, 1.1-3.4; $P = .01$) were significantly associated with response on day +30.

Two of the 3 patients diagnosed with an overlap syndrome were in PR on day 30 and achieved CR by day 60 after inolimomab. One patient is still alive in CR, whereas the other died from progression of Hodgkin's lymphoma. The third patient did not respond to inolimomab and died due to GVHD.

Survival

OS at 6, 12, and 24 months was 34% (95% CI, 24%-44%), 22% (95% CI, 13%-31%), and 18% (95% CI, 10%-26%), respectively (Figure 1). GVHD was the main cause of death, either aGVHD (49%) or chronic GVHD (13%), followed by opportunistic infections (27%). On the other hand, relapse of the underlying disease was the cause of death in only 4% of patients, even among the 42% who responded to inolimomab on day +30 (2 of 39 responders [5%] died from relapse). To analyze the impact of responding to inolimomab on survival, we performed a landmark analysis on day +30 of therapy, including only the 58 patients alive at this time (39 responders and 19 nonresponders). The OS at 6 months and 2 years was higher in responders: 6-month OS 67% (95% CI, 52%-82%) versus 26% (95% CI, 6%-46%) and 2-year OS 33% (95% CI, 18%-48%) versus 20% (95% CI, 1%-40%) ($P = .03$), respectively (Figure 1). Multivariate analysis was not done because of the small patient numbers.

DISCUSSION

In this current single-center study, the use of inolimomab as salvage therapy for steroid-refractory aGVHD was associated with prolonged survival in only 18% of patients and in approximately one-third of day +30 responding patients. The updated results confirm that inolimomab may be an active drug in this setting, with an ORR of 42%-48% on days +30 to +60 of therapy. However, the poor long-term outcomes highlight the importance of reporting long-term results in studies of steroid-refractory aGVHD [7].

Table 2
Univariate and Multivariate Risk Factor Analysis for Response to Inolimomab Therapy by Day +30 after Start of Therapy

Predictors of Day +30 Response				
Variable	CR or PR to Salvage Inolimomab Therapy			
	Univariate Analysis		Multivariate Analysis	
	Day 30 Response (%)	*P*	HR, 95% CI	*P*
EBMT risk index				
Low and intermediate risk (score 0-3)	51	.09	NA	.2
High (score 4-6)	33			
Overall aGVHD grade at inolimomab onset				
II-III	52	.03	HR 1.8, 95% CI 1.06-3	.03
IV	29			
Line of salvage therapy for refractory aGVHD			NT	
First or second	30	.161		
Third or higher	23			
Courses of inolimomab			NT	
One course, 65 (71%)	28	NS		
More than 1 course, 27 (29%)	25			
Lymphocyte count at the start of inolimomab				
$>.3 \times 10^9$/L	51	.089	HR 1.9, 95% CI 1.1-3.3	.02
$\leq.3 \times 10^9$/L	32			
Stage of GI aGVHD at inolimomab onset				
Stage 0-II	52	.09	NA	.08
Stage III-IV	33			
Serum albumin at start of therapy			NT	
≥ 30g/L	49	NS		
<30 g/L	34			
CMV serostatus			NT	
Donor and receptor negative	42	NS		
Donor and/or receptor seropositive	43			
HLA matching				
Mismatch HLA	40	NS	NT	
No mismatch	52			
Onset of inolimomab				
After day 15	54	.021	HR 1.9, 95% CI 1.1-3.4	.01
Before day 15	29			
Year of treatment			NT	
Before 2005	49	NS		
After 2005	37			

HR indicates hazard ratio; EBMT, European Group for Blood and Marrow Transplantation; NA, not available; NT, not tested; NS, not significant; GI, gastrointestinal; CMV, cytomegalovirus; HLA, human leukocyte antigen.

Variables found to improve the day +30 ORR were mostly expected (aGVHD <grade IV, no severe lymphocytopenia, and a trend for nonsevere GI involvement). The improved outcome in patients who started inolimomab therapy more than 15 days after aGVHD onset probably reflects a time-dependent selection bias; patients who survive longer after aGVHD onset and under high-dose steroids may be biologically more fit and/or have a slower-progressing (or less-aggressive) aGVHD. Supportive care has dramatically improved over the past 2 decades, and this surely contributes to the improved short-term outcome in patients who respond to salvage GVHD treatment. However, the outcome of patients with refractory GVHD has not improved over time, and because this was the cause of death in 62% of

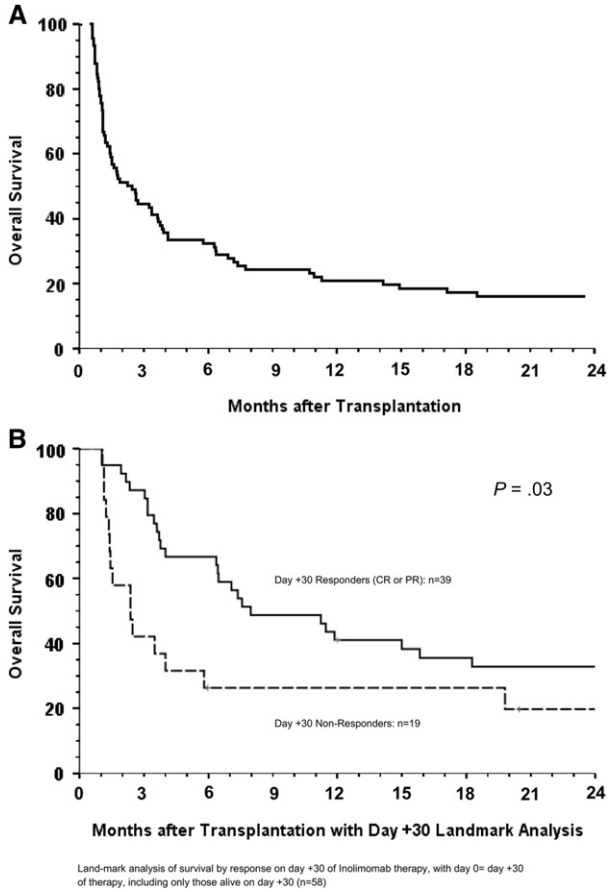

Figure 1. Two-year overall survival (A) for the whole population and (B) for day +30 responders and nonresponders.

patients in our series, we were unable to observe any possible benefit of improved supportive care.

Treatment with inolimomab was well tolerated, as previously reported [10], and the infection-related mortality (27%) was not as high as that observed with other drugs, such as antithymocyte globulin [16]. Of course, it is not possible to attribute severe infections solely to inolimomab, because these much-debilitated patients receive other immunosuppressive agents that contribute to opportunistic infections.

Despite the retrospective nature of the current study, a strong effort was put forth to meet the quality criteria recently considered important in reporting the results of secondary treatment for steroid-refractory aGVHD. In addition, the study was based on a consecutive series of patients who received the same therapy without major changes over time. Table 3 shows the compliance of our study with the 10 quality criteria recently considered important in these studies [7].

The main strengths of our report are as follows: (1) clear definition of inclusion criteria, (2) no exclusion of patients with an Eastern Cooperative Oncology Group performance status >2 or active infection, (3) no changes in inolimomab posology over time, (4) response evaluation at established time points (especially day +30 in our study, due to the predictive value of day +28 response [8,9]) with predefined criteria, (5) exclusion of patients who died before the day of evaluation in the statistical analysis, and (6) estimation of long-term survival.

A limitation of the study is the absence of a control group. In an effort to mitigate this problem, we compared our results with those compiled in the recent extensive review by Martin et al. [7]. Due to the heterogeneity of patients with steroid-refractory aGVHD, a direct comparison of the outcomes reported herein with other studies cannot be made. Nevertheless, inolimomab does not appear to offer any advantage over other reported treatment options. The CR/PR in our study was 42% and 46% on day +30 and +60, respectively, which is similar to the 43% ORR described in a prior phase II study with an anti–interleukin-2 receptor monoclonal antibody [17]. In comparison, the median ORR in

Table 3
Martin Criteria Applied in Our Study

Criteria	Met	Explanation
1. Adequately defined eligibility criteria	Yes	Inclusion/exclusion criteria are defined in Methods. They were maintained unchanged along the time.
2. Minimization of bias in patient selection	No	A possible selection bias cannot be excluded because of the retrospective nature of our analysis. If any, the bias should affect negatively the results, as only those patients affected with refractory mild aGVHD and isolated skin involvement who responded to oral second-line therapy (as MMF or sirolimus) could be lost. Probably the included patients represent the most severe cases, which are the main problem in the clinical setting.
3. Consistent treatment regimen	Yes	All the patients received the same dose, schedule, and duration of inolimomab. Description of concomitant treatment (with the exception of corticosteroids previous days and dosage) is provided and was considered in the response and survival analysis.
4. Objective criteria for organ response	Yes	Objective criteria were used (described in Methods).
5. Unambiguous criteria for overall response	Yes	Stringent criteria were used for overall response, consisting of a global reduction of at least 1 grade in the overall evaluation without impairment in any organ. Patients with improvement in 1 organ but deterioration in another were classified as progression (detailed in Methods).
6. Prespecified time for response assessment	Yes	Response was reevaluated every week. Following the new recommendations, we analyzed the response by day +30. Deaths, relapses, and introduction of other therapies were considered and included as competitive events in the analysis.
7. Concomitant treatment taken into account	Yes	Use of new immunosuppressants after the enrollment was considered as treatment failure.
8. Well-established control benchmark	No	No control could be used. Historical cohort of patients who received other second-line agents cannot be used because support therapy deeply changed in the last 10 years.
9. Statistical hypothesis and power estimate	NA	Not applicable due to the retrospective nature of the study.
10. Survival	Yes	Survival at 6 months and 1 and 2 years from the onset of the study is shown.

MMF indicates mycophenolate mofetil; NA, not applicable.

the 29 studies included in a recent review [7] was 58%. In addition, the CR rate found in the current study compares poorly with the 32% median CR rate observed in prior studies, with a 95% CI of 20%-40%, and thus our 14% CR rate is lower than the estimated 95% CI of prior pooled studies. The same is applicable to the 6-month OS rate; in the review by Martin et al. [7], the median 6-month OS rate was 49% (95% CI, 40%-60%). Again, our observed 6-month OS rate of 34% (95% CI, 24%-44%) also seems statistically poorer than those observed with other drugs. Of course, our "worse-than-expected" outcomes are surely influenced by the real-life clinical use of inolimomab in the current study, thus including very sick patients who would have been excluded from prospective trials or observational studies [5,6].

In conclusion, although inolimomab is a well-tolerated drug in patients with refractory aGVHD, its activity does not seem better than reported with other drugs. More important, long-term survival in this large series of patients appears to be very low. Whether results can be improved with currently available treatments is uncertain, and efforts should be directed in participating in clinical trials testing novel therapeutic approaches.

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