Safety and Clinical Effect of Subcutaneous Human Interleukin-21 in Patients with Metastatic Melanoma or Renal Cell Carcinoma: A Phase I Trial

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Abstract

Purpose: This phase I study in patients with metastatic melanoma (MM) and renal cell carcinoma (RCC) evaluated the safety and maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of s.c. treatment of human recombinant interleukin 21 (IL-21).

Experimental Design: Phase I dose-escalation trial with treatment of three to six patients at each dose level, escalating from 3 to 300 μg/kg. Treatment was administered s.c. on an outpatient basis 3 days per week for 8 or 16 weeks.

Results: Twenty-six patients entered the study. Recombinant IL-21 was generally well tolerated, and dose-limiting toxicities (DLT) were first seen at dose levels of 200 and 300 μg/kg. The following four DLTs were observed in three patients: increased transaminases, increased hyperbilirubinemia, hypersensitivity reaction, and lethargy. The MTD was declared to be 200 μg/kg, although five of seven patients at the 300 μg/kg dose level experienced no DLTs. A treatment-related effect on soluble CD25 was observed at all dose levels and increased with dose level. Furthermore, higher doses induced interferon-γ, perforin, and granzyme B mRNA expression in peripheral blood, and granzyme B protein expression in both CD8⁺ T cells and natural killer cells, consistent with the activation of cytotoxic lymphocytes. Three patients, one patient with MM and two with RCC, obtained a partial response.

Conclusion: Outpatient treatment with s.c. administered IL-21 was tolerated and had dose-dependent pharmacodynamics. rIL-21 showed antitumor activity in patients with MM and RCC. Clin Cancer Res; 16(21); 5312–9. ©2010 AACR.

Although treatment of patients with metastatic melanoma (MM) and renal cell carcinoma (RCC) is generally non-curative, a minority of patients can be cured with treatment strategies modulating the immune system as interleukin 2 (IL-2) and interferon (IFN)-α are capable of inducing complete responses (CR) in a small fraction of these patients (1, 2). However, the use of these agents is hampered by low response rates and treatment-associated toxicities.

IL-21 is a cytokine with some sequence similarities to IL-2 and IL-15, and is produced primarily by activated CD4⁺ T cells, activated natural killer T (NK-T) cells, and follicular T helper cells (3–5). The IL-21 receptor is expressed by immune and some nonimmune cell types and is upregulated on NK, B, and T cells after activation (4). This pattern of expression suggests that the primary effects of recombinant IL-21 (rIL-21) are immunomodulatory, a hypothesis that has been supported by in vitro and in vivo analyses (6, 7). The activities of IL-21 include effects on both lymphoid and myeloid cell lineages. IL-21 stimulation of T, B, and NK cells leads to enhanced proliferation and maturation of the effector function (8). The effect of IL-21 on the monocyte/macrophage and dendritic cell response are less well characterized; however, it seems that IL-21 stimulates antigen uptake, protease activity, and survival and induction of CD4⁺ T-cell proliferation (9, 10). Human rIL-21 is now available for clinical use. rIL-21 enhances antitumor activity in animal models through at least two different cell types. It enhances tumor-specific cytotoxic T lymphocyte (CTL) responses by increasing proliferation, survival, and specific killing ability of T cells (11). rIL-21 also matures and enhances the lytic activity of NK cells through a perforin-dependent mechanism (12). Unlike IL-2, rIL-21 renders CD4⁺ T cells resistant to regulatory cell suppression and does not stimulate proliferation of regulatory T cells (13). The half-life of rIL-21 is ~1 to 3 hours following i.v. administration. The human safety profile of rIL-21 when administered i.v. has been assessed in two

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phase I trials (12, 14). rIL-21 has been well tolerated i.v. at doses up to 30 μg/kg with the different treatment schedules being used. Because the safety profile obtained with i.v. administration indicates that rIL-21 could be developed for self-administration in an outpatient setting, the current trial was designed to describe the safety and tolerability of s.c. administration of rIL-21. This administration of the cytokine would provide additional options for patients in selecting future treatment combinations.

The purpose of this trial was to test the safety and tolerability and to estimate the maximum tolerated dose (MTD) of s.c. rIL-21 administration in patients with MM and RCC. Further, the purpose was to evaluate pharmokinetics and pharmacodynamics of rIL-21 and to assess preliminary antitumor activity.

Materials and Methods

Recombinant IL-21

Novo Nordisk provided the rIL-21 for the study. rIL-21 is expressed in Escherichia coli, resulting in a NH2-terminal methionylated form. ZymoGenetics developed the processes in the production, refolding, and purification of the molecule as well as analytic methods for assessment of purity and potency. Manufacturing was done in accordance with good manufacturing practices at the facilities of Avecia, Billingham, United Kingdom.

Study design

The primary objective of the trial was to assess the safety and tolerability of escalating doses of rIL-21 and to determine the MTD by dose escalation. Secondary objectives were to characterize the dose-response relationship for different biomarkers, to determine the pharmokinetics of rIL-21 following s.c. administration, to determine the frequency of anti-rIL-21 antibody induction during therapy, and to measure effects of rIL-21 on tumor size. Safety and tolerability were assessed using the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Dose escalation was conducted using a standard 3 + 3 design, with a starting dose of 3 μg/kg and escalating doses of 10, 30, 100, 200, and 300 μg/kg until the MTD was determined. Dose-limiting toxicity (DLT) was defined as toxicity ≥ grade 3 being probably or definitely correlated to study drug, except for the following toxicities: grade 3 fever, grade 3 asymptomatic hyperglycemia, grade 3 and 4 hyperuricemia, grade 3 lymphopenia (<0.5 × 10^9/L) ≤ 7 days, and grade 3 neutropenia ≤ 5 days.

rIL-21 was administered s.c. at the anterior site of the thigh in the morning, 3 days per week for 8 weeks. Subjects were hospitalized for 24 hours after the first dose administration and after a later dose during week 5 to permit pharmokinetics, hematology, and body temperature assessments. Subjects with no symptomatic tumor progression after 8 weeks of treatment were offered to continue treatment at the same dose level for an additional 8 weeks. The maximum duration of the trial was 16 weeks. Patients with clinical benefit after 16 weeks were offered continued treatment outside the protocol. Escalation from one dose level to the next was allowed only when the third subject in a cohort had completed 3 weeks of treatment, all safety data from the three subjects had been evaluated, and dose escalation was recommended by the study dose evaluation group. All patients exposed to rIL-21 were evaluable for toxicity. Computed tomography (CT) or magnetic resonance scans for tumor evaluation per Response Evaluation Criteria in Solid Tumors were done at baseline and at the end of each 8-week cycle (15).

Patients

Eligible patients had histologically verified, surgically incurable MM or RCC, for whom previous systemic treatments were allowed. Other inclusion criteria were as follows: age of 18 years or older, Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 3 months, adequate bone marrow function (WBC ≥ 2.5 × 10^9/L, absolute neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, hemoglobin ≥ 6.2 mmol/L with no signs of hemolytic anemia, and lymphocytes ≥ 0.8 × 10^9/L), S-creatinine ≤ 177 μmol/L, bilirubin ≤ 26 μmol/L, aspartate aminotransferase ≤ 100 IU/L, alanine aminotransferase ≤ 100 IU/L (unless attributable to liver metastases, in which case ≤ 200 IU/L), lactate dehydrogenase (LDH) ≤ 500 IU/L, and use of effective contraception. Key exclusion criteria were as follows: central nervous system metastases; radiotherapy less than 4 weeks before start of treatment; systemic treatment for stage IV disease less than 4 weeks before start of treatment; treatment with anti–CTLA-4 monoclonal antibodies less than 12 weeks before start of treatment; documented positive serologic testing for hepatitis B or C within a year before start of treatment; clinically uncontrolled infectious disease including human immunodeficiency virus or acquired immune deficiency syndrome–related illness; uncontrolled hypercalcemia; history of or active presence of autoimmune diseases (except vitiligo and treated pernicious anemia); history of
any other active malignancy including ocular melanoma (except basal cell carcinoma of the skin and cervical cancer in situ) within 5 years before enrollment; any significant systemic disease, which according to the investigator could compromise the safety of the patient or interfere with the trial objectives; concurrent treatment with systemic corticosteroids (topical or inhaled corticosteroid treatment was permitted); and pregnant, breast-feeding, with the intention of becoming pregnant, or not using adequate contraceptive measures. A written informed consent was obtained from each patient. The study was carried out in accordance with criteria of Good Clinical Practice (EUDRACT no. 2006-000376-32).

The study was carried out between July 2006 and August 2008. Patients were treated in the oncologic centers of Aarhus University Hospital and Herlev Hospital (both in Denmark), and In St James’s University Hospital, Leeds (United Kingdom). Patients provided written consent before entering the trial. The local ethics committee as well as the Health Authorities in Denmark and the United Kingdom approved the trial.

All clinical laboratory tests as well as the soluble CD25 (sCD25) analysis were done centrally by Esoterix Clinical Trial Services, Belgium. Analyses of IFN-γ, perforin, granzyme B mRNA, and pharmacokinetics were done by Novo Nordisk.

Analyses of anti–rIL-21 antibodies were done by Covance Laboratories Ltd.

Pharmacokinetics

On the first dosing day and during week 5 (on days 31 or 33), blood samples were drawn for pharmacokinetic assessment at the following time points: predose; 10 and 30 minutes; 1, 2, 3, 4, 5, 6, 8, 12, 18, and 24 hours. Two aliquots of 250 μL serum each were prepared and stored at −70°C until analysis. Serum was analyzed by use of a rIL-21 enzyme-linked immunosorbent assay (ELISA). ELISA was validated for human serum samples. Analyses were done as previously reported (12).

Pharmacodynamics

Absolute (TruCount) and relative amounts of NK, T-cell, and B-cell subsets were assessed by flow cytometry (FACSCalibur) at Esoterix Clinical Trial Services, Belgium. Data were processed in CellQuest.

Expression of IFN-γ, perforin, and granzyme B mRNA was determined, as previously described, by quantitative reverse transcriptase-PCR (RT-PCR) of PBMC samples collected at predose on day 1 as well as on days 2 and 5 (16).

For granzyme B protein expression, peripheral blood mononuclear cells were purified from whole blood by density gradient centrifugation using Lymphoprep (Axis- Shield), and NK cells and CD8+ T cells were purified using magnetic immunoselection reagents (Miltenyi Biotec). Granzyme B was detected by immunoblotting as previously described (17). This analysis was only done for the six patients enrolled in Leeds. Serum samples were collected at the following time points and stored at −70°C until analysis: predose; 4 and 24 hours postdosing; days 3 and 5; and predose on three different days in weeks 3, 5, and 7 of treatment. sCD25 was analyzed using a sandwich ELISA (Quantikine, DR2A00, R&D Systems) at Esoterix Clinical Trial Services, Belgium.

Serum antibodies specific for rIL-21 were measured by ELISA at days 1, 15, 29, 54, and 131. Analyses were done as previously described (12).

Results

Patients

A total of 26 patients (13 MM and 13 RCC) were included in the study. Patients included 10 women and 16 men between 28 and 80 years of age (median age 59 years). The patient and cancer characteristics are summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tr>
<td>No. of patients</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (62)</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Median</td>
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<td>Range</td>
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<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Melanoma patients</td>
<td>13 (50)</td>
</tr>
<tr>
<td>AJCC* †</td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>5 (38)</td>
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<tr>
<td>M1b</td>
<td>4 (31)</td>
</tr>
<tr>
<td>M1c</td>
<td>4 (31)</td>
</tr>
<tr>
<td>RCC patients</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Motzer criteria* ‡</td>
<td></td>
</tr>
<tr>
<td>Good prognosis</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Intermediate prognosis</td>
<td>6 (48)</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>0</td>
</tr>
<tr>
<td>Prior systemic treatment for metastatic disease</td>
<td></td>
</tr>
<tr>
<td>Any IL-2</td>
<td>20 (77)</td>
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<tr>
<td>Any other systemic treatment</td>
<td>5 (19)</td>
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</tbody>
</table>

Abbreviation: AJCC, American Joint Committee on Cancer.

*Stage at time of inclusion.

†M1a, distant skin, subcutaneous, or lymph node involvement with normal serum LDH; M1b, lung metastases with normal serum LDH; M1c, all other visceral metastases or an elevated serum LDH.

‡Motzer criteria is based on a score of the following five risk factors; hemoglobin, LDH, corrected serum calcium, time from diagnosis to systemic treatment, Karnofsky performance status. Good prognosis is 0 risk factor, intermediate is 1 to 2 risk factors, and poor prognosis is 3 to 5 risk factors.
Four patients were withdrawn during the study, three patients due to adverse events and one patient due to rapid progression of the disease. The remaining 22 patients completed the first 8 weeks; of these, 19 continued treatment after week 8. One patient was withdrawn due to adverse event in this part of the trial, and the remaining 18 subjects completed the 16 weeks of treatment.

### Safety and toxicity

An overview of all treatment-emergent adverse event is presented in Table 2. During the entire trial, 674 adverse events were reported in the patients. Increased numbers of adverse events were reported with escalating doses of rIL-21. The majority of adverse events were of severity grade 1 (62%) followed by grade 2 (32%). Fifteen patients reported 35 adverse events of grade 3 severity, and two patients experienced adverse events of grade 4 severity. Of the 674 adverse events, three subjects reported five serious adverse events: Two subjects in the 200 μg/kg group had three serious adverse events and one subject in the 300 μg/kg dose group had two serious adverse events. No treatment-related deaths were observed in this trial.

The most commonly reported adverse events were nausea, vomiting, pyrexia, fatigue, injection site reaction, myalgia, arthralgia, headache, pruritus, and rash, which were all observed in at least 20% of subjects exposed. Injection site reaction was observed in 58% of subjects (15 patients). No apparent relation of injection site reaction to escalating doses of rIL-21 was observed, and most injection site reactions were transient, indolent, and not nodular in presentation.

The most commonly reported adverse events of grade 3 and 4 considered possibly or probably related to rIL-21 were hematologic abnormalities (anemia, thrombocytopenia, lymphopenia, and neutropenia), hyperuricemia, and pyrexia. Most of these adverse events, considered related to rIL-21, were reported in the 200 and 300 μg/kg rIL-21 dose groups. Human rIL-21 was withdrawn from four subjects due to adverse events (increased transaminases, increased hypersensitivity reaction, arthralgia, and lethargy). In the subject experiencing increases in transaminases, this...
adverse event occurred abruptly on days 38 to 40 of treatment. The maximum alanine aminotransferase observed was 692 U/L, with fast normalization after rIL-21 treatment was stopped.

Dose escalation

Human rIL-21 was tolerated at the 3, 10, 30, and 100 μg/kg dose levels with no DLT. One subject exposed to 200 μg/kg rIL-21 experienced three DLTs (increased transaminases, hyperbilirubinemia, and anemia, all grade 3), leading to expansion at this dose level to a total of six subjects. In the 300 μg/kg dose group two DLTs were reported in two of seven patients. The DLTs were drug hypersensitivity (grade 3) and lethargy (grade 3) evaluated to be definitely related to rIL-21. Thus, although higher doses were tolerated by some patients, 200 μg/kg was declared the MTD for this s.c. regimen.

Pharmacokinetics

The mean serum rIL-21 concentrations versus time profiles after the initial dose are presented in Fig. 1. Pharmacokinetics following the initial dose showed a dose-dependent increase in \( C_{\text{max}} \) and area under the curve. The mean half life ranged from 3.6 to 5.2 hours, and the mean time to maximum concentration (\( t_{\text{max}} \)) was within the range of 0.3 to 1 hour. Pharmacokinetics evaluation of week 5 concentration versus time, after the patient had received multiple rIL-21 doses, showed that the mean half life (2.5-3.4 hours) and \( t_{\text{max}} \) (0.3-2.5 hours) were consistent...
with those obtained after the initial dose. Although an assessment of IL-21 bioavailability from s.c. dosing was not a part of this study, comparing the serum concentration data obtained here with previously reported data from i.v. administration studies of IL-21 (12, 14) suggest the systemic bioavailability to be low (less than 10%) when IL-21 is administered s.c.

**Pharmacodynamics**

Significant redistributions of NK, T, and B cells were observed, as assessed by acute drops in absolute numbers of NK cells (CD3+/CD56+), cytotoxic T cells (CD3+/CD8+), T-helper cells (CD3+/CD4+), and B cells (CD19+) in peripheral blood (data not shown). We also measured sCD25, as a marker of immune activation, multiple times during this trial. sCD25 is a subunit of the IL-2 receptor cleaved off from activated T and NK cells. The levels of sCD25 increased slightly with 3, 10, and 30 μg/kg rIL-21 dose regimens. Higher increases in sCD25 levels following treatment with rIL-21 were observed for 100, 200, and 300 μg/kg rIL-21 dose regimens. The mean serum soluble sCD25 curve is presented in Fig. 2. The drop observed at day 56 was due to a short dosing cessation between the main and the extension trial observed in most subjects.

mRNA levels of the important effector molecules, IFN-γ, perforin, and granzyme B, in peripheral blood mononuclear cells were measured in the 5 days following administration of rIL-21 for each of the six dose levels (Fig. 2B). These data show significant biological activity of rIL-21 at the higher doses. IFN-γ is a cytokine produced by NK cells and CTLs as part of the innate immune response. Perforin is released by CD8 T cells and NK cells along with granzyme molecules; perforin facilitates the entry of the proapoptotic granzymes into the target cells, resulting in apoptosis induction. Granzyme B is a particularly potent proapoptotic protease, and its expression is a surrogate biomarker of cytotoxic activity (17). Expression of granzyme B is induced by cytokine stimulation. Purified populations of CD8+ T cells and NK cells from patients receiving 200 and 300 μg/kg IL-21 showed induction of the granzyme B protein (by immunoblotting; Fig. 2C), consistent with the activation of cytotoxic lymphocytes. Specific anti–rIL-21 antibodies were observed in 7 of 26 patients at some point in time during the trial; none of these antibodies had neutralizing activity. In two of these seven patients, anti–rIL-21 antibodies were detected at baseline.

**Antitumor effect**

Of the 26 patients included in the trial, all patients were evaluable for tumor response at week 8 and 19 patients at week 16. One patient progressed early clinically, and a week 8 CT scan was therefore not done. The overall best tumor response was 3 patients with partial response (PR). Fifteen patients had stable disease (SD), and 8 had progressive disease (PD). The overall disease control rate (CR + PR + SD) was 69%. None of the patients had previously received treatment with CTLA-4 antibodies.

The partial responders included one patient with melanoma and two with RCC. The maximal changes in the sum of longest diameters are shown in Fig. 3. Although the study was not designed to evaluate duration of response, responses lasted from 6 to 15 months in the three patients with PR. The two RCC patients with PR received extended treatment with rIL-21 outside protocol. The third patient achieving an objective response was an 80-year-old male with melanoma who was treated with 10 μg/kg. This patient had not received any prior treatment for MM. The patient could not receive extended treatment with rIL-21 due to surgery for a previously known aortic aneurism. This patient actually showed a 100% response, but the confirmation scan was done before day 28 and therefore the patient was classified as having a PR instead of a CR, per the Response Evaluation Criteria in Solid Tumors criteria.

Figure 4 shows the baseline and posttreatment CT scans for one of the patients with a clinical response. This patient, a female with metastatic RCC, was previously treated with IL-2/IFN and later sorafenib with progression on both regimens. The patient received 30 weeks of rIL-21 treatment in total, and it was eventually possible to excise the residual tumor. The patient later had a local relapse, which was surgically removed, and now has no evidence of disease. The third partial responder had previously been treated with IL-2/IFN and had a PR in lung and mediastinal lymph nodes.

**Discussion**

This study suggests that outpatient treatment with s.c. administered rIL-21 in patients with MM and RCC is generally safe and has promising antitumor activity. The most common adverse events, such as flu-like symptoms and rash, were mild or moderate in severity. The most common laboratory anomalies were similar to those observed with IL-2. Severe toxicities, such as capillary leak syndrome or central nervous system toxicity associated with IL-2 or...
IFN-α, were not observed with the doses of rIL-21 administered in this study. To date, two phase I trials and one phase II trial in MM and RCC had been published (12, 14, 16). These studies showed that i.v. administered rIL-21 was safe up to 30 μg/kg, although doses up to 100 μg/kg were well tolerated in some patients. Furthermore, a recent phase II trial in MM using i.v. IL-21 has shown a promising response rate of 23% in 40 patients (18).

In this study with s.c. rIL-21, a dose of 200 μg/kg was declared to be the MTD. In the 300 μg/kg dose group, two DLTs were reported: one patient with drug hypersensitivity and one patient with lethargy, both grade 3. Five other patients tolerated 300 μg/kg well. It can be argued that drug hypersensitivity may not be a true DLT, as this event could in theory occur with any dose. Furthermore, lethargy is a very well known toxicity with cytokines and disappears when treatment is discontinued. Therefore, treatment with rIL-21 at doses higher than 200 μg/kg s.c. may prove feasible in future studies.

rIL-21 showed promising antitumor activity in this phase I study, with 18 of 26 evaluable patients achieving an overall response of SD or better, among them three patients with PR. These results are comparable with two previously published phase I studies with rIL-21. In those phase I trials, 2 CR and 20 SD were observed in 53 melanoma patients, and 4 PR and 13 SD were observed in 19 RCC patients (12, 14). Furthermore, a phase II trial in melanoma showed 1 CR and 1 PR in 24 patients (16).

The majority of the patients had previously received IL-2 as part of their treatment. It is known that in addition to stimulating T-effector cells, IL-2 also stimulates T-regulatory cells, suggesting a potential negative influence on T-cell immunity (19, 20). A recent article suggests that IL-21 enhances T-cell immunity through increased effector CD8+ cells and decreased CD4+ regulatory cells in the tumor microenvironment (13). This could explain why some patients who progressed on IL-2 had an objective response with rIL-21 treatment.

Previous studies done in vitro have shown that IL-21 increases the expression of granzyme B mRNA and protein in NK cells (21). Furthermore, expression of granzyme B mRNA was induced by IL-21 treatment in vivo (12, 16, 22). Our data show that although there was little evidence of granzyme B protein expression in patients at 5 days following administration of one of the lower doses of rIL-21, substantial granzyme B expression was induced following administration of doses of 200 and 300 μg/kg (Fig. 2E).

Similar trends were found for mRNA levels of IFN-γ and perforin. These trends probably correlate with activation of cytotoxic lymphocytes in these patients. None of the biomarkers examined showed an association with treatment response. However, the low number of patients in this phase I trial with response does not allow for extensive analyses of predictive biomarkers.

In conclusion, our data show that multiple dosing of s.c. rIL-21 can be administered in an outpatient setting with acceptable toxicity, and that rIL-21 has a promising antitumor effect in both MM and RCC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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