CONIFER - Non-interventional study to evaluate therapy monitoring during Exjade® treatment of iron toxicity in MDS patients with transfusional iron overload in the course of treatment

Zielsetzung/Fragestellung

patients with transfusional iron overload by monitoring serum ferritin concentrations and iron concentrations in the liver. In addition to serum ferritin concentrations, the study investigated Exjade® doses, the amount of blood transfusions, i.e., iron uptake, therapy compliance, and safety and tolerability of Exjade® treatment.

Indikation

Patients with MDS

Wirkstoff

Deferasirox

Marke/Handelsname

Exjade®

Anzahl der vorgesehenen Studienzentren/Praxen in Deutschland

74

Angestrebte Fallzahl beteiligter Patienten

250

Beginn der Studie

01.01.2010

Geplante Dauer der Studie

Recruitment till January 2012; observational period 2 years till January 2014

Studiennummer

CICL670ADE09

Unternehmen

Novartis Pharma GmbH
Roonstr. 25
90429 Nürnberg
Deutschland

Stand der Information

16.06.2015

Status der Studie

Study completed

Zusammenfassung der Ergebnisse

Methodologie
This is a non-interventional study (NIS) in patients with MDS who are treated with Exjade® according to the facility’s regular treatment protocols and in accordance with the product information. Exjade® may not be prescribed for the purpose of including the patient in the NIS. Assessment intervals per patient are not fixed but should be scheduled according to facility procedure and each patient’s clinical symptoms. The medical decision about therapeutic or diagnostic measures is made solely by the treating physician. No further tests are required apart from routine clinical examinations.

Analysierte Anzahl der Patienten
99

Diagnose und Einschlußkriterium
MDS patients 18 years or older with transfusional iron overload and decision taken by the treating physician to prescribe Exjade® were included in the study. The diagnosis was made at the discretion of the attending physician, according to his/her medical practice.

Wirkliche Dauer der Studie
4.5 years

Wirksamkeit unter Alltagsbedingungen
As opposed to controlled clinical trials, a NIS is not designed to prove the efficacy and tolerability of a medication, but can provide information on the application in real-life settings. The objective of this non-interventional post-marketing surveillance study was to evaluate Exjade® treatment in MDS patients with transfusional iron overload by monitoring serum ferritin concentrations and iron concentrations in the liver. In addition to serum ferritin concentrations, the study investigated Exjade® doses, the amount of blood transfusions, i.e., iron uptake, therapy compliance, and safety and tolerability of

Sicherheit

Adverse Event (AE)
An “adverse event” (AE) was defined as every untoward medical condition occurring in a patient after the administration of a drug or treatment, irrespective of whether or not a causal relationship with the drug or treatment was suspected (4th Announcement on the Reporting of Adverse Events and Drug Abuse according to Section 63b(1-8) of the German Drug Law). All AEs occurring in patients had to be documented on the "Adverse Event Report", including the type of the event, its first occurrence and its duration.
Furthermore, the doctor had to document whether or not he suspected a relationship to any of the drugs or treatments the patient had received. Additionally, he was required to report countermeasures taken as well as the outcome of the event.
Serious Adverse Events (SAE)
Using the definitions denoted in §3 Par. 8 of the Guidelines for Good Clinical Practice, GCP, (dated August 9th, 2004), a serious adverse event (SAE) is any untoward medical occurrence which
• Is fatal or life-threatening,
• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability or incapacity
• Results in a congenital anomaly or a birth defect.
Hospitalization was not regarded as a SAE, if one of the following conditions applied:
• Hospitalizations which had already been scheduled prior to inclusion in the NIS.
• Elective hospitalization for the treatment of pre-existing conditions which were not related to the disease investigated in the NIS or the drug applied during the NIS.
• Outpatient hospital treatment which did not result in hospitalization (unless one of the other criteria is met, e.g., the event is life-threatening).
• Hospitalizations which were part of the regular treatment or monitoring of the disease investigated in the NIS and have not been caused by a deterioration of the patient’s condition.

Methoden
any data were collected and assessed.

The NIS was conducted by resident hemato-oncologists as well as practising physicians in the clinic in Germany. Male and female patients with diagnosed with MDS, who were being treated with Exjade® and for whom treatment with Exjade® was medically indicated, were allowed to be included in the study. It was not allowed to prescribe Exjade® only for the purpose of the NIS but not for clinical necessity. Data collection visits were scheduled at the beginning of the study and subsequently after 3, 6, 9, 12, 18 and 24 months.

Ergebnisse zur Wirksamkeit unter Alltagsbedingungen

Change of Serum Ferritin: Table 9.4.7 shows an increase in the mean concentration from baseline (2075 ± 1253 µg/L) to the 3rd follow-up visit (2475 ± 2031 µg/L), followed by a decrease to baseline level by the 6th follow-up visit (2067 ± 1532 µg/L). In an explorative analysis the serum ferritin levels from Table 9.4.7 were stratified by different doses of Exjade®. Stratification by a baseline Exjade® dose of <1000 mg vs. ≥1000 mg, i.e., independent of body weight, showed a trend towards serum ferritin reduction at the higher dose and no reduction at the lower dose, while stratification by a baseline dose of <15 mg/kg vs. ≥15 mg/kg showed a clear serum ferritin reduction at the higher dose and again no reduction at the lower dose. Ferritin levels were further stratified by doses of <15 mg/kg vs. ≥15 mg/kg in the course of the study (Figure 9.4.4) as well as doses of <20 mg/kg vs. ≥20 mg/kg in the course of the study. In both stratifications the higher initial levels of serum ferritin were reduced at the highering.

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- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or a birth defect.

Hospitalizations which were part of the regular treatment or monitoring of the disease investigated in the NIS and have not been caused by a deterioration of the patient’s condition.

Elsevier, 1992; 585-589) can be performed. In this study the iron status of only very few patients was determined by these methods. In this NIS the low frequency of using alternative methods besides determining iron concentration and iron overload via serum ferritin potentially shows, that these methods are still not routinely used for MDS diagnostics potentially due to additional complexity, additional costs and limited technical availability (Mitchell M, Ther Adv Hematol 2013; 4(2):93-102). Safety evaluation comprised the documentation and analysis of treatment-emergent AEs/SAEs. Overall, 80/99 of the patients (80.81%) in this NIS experienced at least 1 AE or SAE, and in 33/99 of the patients (33.33%), at least 1 of these events was drug-related. Considering only the non-serious, drug-related AEs, the most frequent AEs were “decrease of creatinine renal clearance” (14 patients or 14.14%) and “diarrhea” (13 patients or 13.13%). All other non-serious, drug-related AEs were “decrease of creatinine renal clearance” (14 patients or 14.14%) and “diarrhea” (13 patients or 13.13%). All other non-serious, drug-related AEs were “decrease of creatinine renal clearance” (14 patients or 14.14%) and “diarrhea” (13 patients or 13.13%).

Ergebnisse zur Sicherheit

As assessed by the treating physicians and shown in Table 9.6.1, the majority of patients (n=80/99, 80.81%) were affected by at least one adverse event (AE) of any nature. Drug-related AEs occurred in 33/99 patients (33.33%). Assessment of drug-related is based on the causality as reported by the physician. Of the 62 patients (62.63%) with serious AEs, 15 patients (15.15%) had serious drug-related AEs. 32 patient (32.32%) deaths were recorded in the study, 2 of which were assessed to be drug-related (see case narratives in Appendix F). In patients with AEs, the number of AEs of any nature was most frequently 1 per patient (Table 6.3 in the Appendix). Of the 355 AEs that occurred altogether, 76 (21.41%) were drug-related, 193 (54.37%) were serious and 30 (8.45%) were serious drug-related AEs (Table 9.6.2). The four most frequently affected primary system organ classes (SOCs) were “investigations” (47.47%), “general disorders and administration site conditions” (30.30%), “infections and infestations” (26.26%), “diabetes” (13 patients or 13.13%). All other non-serious, drug-related AEs were “decrease of creatinine renal clearance” (14 patients or 14.14%) and “diarrhea” (13 patients or 13.13%).

Hospitalization was not regarded as a SAE, if one of the following conditions applied:

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
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Schlussfolgerungen
This non-interventional post-marketing surveillance study was performed to evaluate characteristics of MDS patients as well as safety of deferasirox (Exjade®) treatment under daily-life conditions. Moreover, a particular focus was set on the concentration of serum ferritin levels as a parameter of iron overload before and after enrollment as well as dosing and duration of deferasirox treatment. The data of 136 patients of either sex at an average age of approximately 72.5 years (mean) were documented at 41 sites. Thereof 99 patients were valid for analysis. The age spectrum (42-88 years) correlates to the age group distribution observed for MDS patients in Germany (Gattermann N, Eur J Haematol. 2013; 91(6):473-482), so the study is representative of the patients treated in practice. The number of transfusions per month and therefore the average iron uptake per month from blood transfusions showed a constant increase during study treatment. A possible cause for this increase could be the progression of the disease over time with decreasing haemoglobin levels due to worsening hematologic function. Although the duration of treatment was relatively long (mean 15.7 ± 8.6 month) compared to other studies (Gattermann N, Haematologica 2012; 97(9):1364-1371) serum ferritin levels and thus iron overload were only decreased in the course of the study when daily deferasirox dosing was ≥15 mg/kg while patients who received <15 mg/kg deferasirox showed no decrease in serum ferritin. Similar results were seen for a dosing of ≥20 mg/kg vs. <20 mg/kg. This leads to the conclusion that the reduction of serum ferritin can only be achieved when an adequate dose of deferasirox is administered. To obtain a more exact measure of iron concentration and iron overload a liver biopsy, MRT (Jensen PD, Mr J Haematol 2004; 124:697-710) and/or SQUID (Brittenham GM, N Engl J Med 1982; 307:1671-1675 and Fischer R, Elsevier, 1992; 585-589) can be performed. In this study the iron status of only very few patients was determined by these methods. In this NIS the low frequency of using alternative methods besides determining iron concentration and iron overload via serum ferritin potentially shows, that these methods are still not routinely used for MDS diagnostics potentially due to additional complexity, additional costs and limited technical availability (Mitchell M, Ther Adv Hematol 2013; 4(2):93-102). Safety evaluation comprised the documentation and analysis of treatment-emergent AEs/SAEs. Overall, 80/99 of the patients (80.81%) in this NIS experienced at least 1 AE or SAE, and in 33/99 of the patients (33.33%), at least 1 of these events was drug-related. Considering only the non-serious, drug-related AEs, the most frequent AEs were “decrease of creatinine renal clearance” (14 patients or 14.14%) and “diarrhea” (13 patients or 13.13%). All other non-serious, drug-related AEs occurred at rates <5.1%. Sixty-two patients (62.63%) experienced SAEs, which were rated as drug-related in 15 (15.15%) patients. Drug-related SAEs were most frequently “decrease of renal clearance” (13 patients or 13.13%) and “increase of blood creatinine” (4 patients or 4.04%). Thirty-two patients (32.32%) died during this NIS while two of these deaths could be related to deferasirox. In conclusion, these AEs/SAEs were in line with the SmPC for Exjade® (Adams RL, The Adv Hematol; 2013; 4(2):93-102). As opposed to controlled clinical trials, a NIS is not designed to prove the efficacy and tolerability of a medication, but can provide information on the application in real-life settings. Exploratory analyses revealed that particularly...