1.0 Abstract

Title

Impact of adalimumab (Humira®) t**h**erapy on **o**cular inflammation, selected health care resource utilization and **p**atient r**e**ported outcomes in patients with active non-infectious intermediate, posterior and panuveitis in routine clinical practice – **HOPE**

Keywords

Adalimumab (Humira®), Non-infectious intermediate, posterior and panuveitis

Rationale and Background

Uveitis is a complex intraocular inflammatory disease that results from several etiologic entities, which in total has been estimated to cause approximately 10% of blindness.

Based on VISUAL I and VISUAL II study data, adalimumab (Humira®) received approval for the treatment of non-infectious intermediate, posterior and panuveitis (NIIPPU) in patients inadequately treated with corticosteroids, in those who require steroid sparing, and in those in whom corticosteroids are inappropriate, from the European Medicines Agency (EMA) in June 2016. The U.S. Food and Drug Administration (FDA) granted adalimumab (Humira®) orphan drug designation for chronic non-infectious uveitis, and in June2016 adalimumab (Humira®) received U.S. approval to treat adults with non-infectious intermediate, posterior and panuveitis.

The term “NIIPPU quiescence” was introduced in order to better fulfill the needs of external audience such as payer and non-ophthalmologist healthcare professionals when evaluating the effect of adalimumab (Humira®) in the treatment of NIIPPU. Frequency of quiescence was evaluated in the post-hoc analyses of VISUAL I and VISUAL II studies, where quiescence and steroid free quiescence as very stringent measures of controlled inflammation were more often achieved with adalimumab (Humira®) than with placebo. Also during the open-label extension in VISUAL-III study, patients with active uveitis at study entry who received adalimumab (Humira®) therapy were likely to achieve quiescence, improve visual acuity, and reduce their daily uveitis-related systemic corticosteroid use. Most patients with inactive uveitis at study entry sustained quiescence without a systemic corticosteroid dose increase.[1]

Although two randomized, controlled studies conducted with adalimumab (Humira®) established the efficacy and safety of adalimumab (Humira®) in NIIPPU indication, very limited data are available on the effect of adalimumab (Humira®) on NIIPPU in

routine clinical setting according to the approved indication and dosage using quiescence as primary endpoint.

In addition, there is a need to have broad data on disease characteristics, etiology, underlying systemic diseases, patient flow and current management practices in NIIPPU.

There is no published data on the impact of adalimumab (Humira®) therapy on hospitalizations and outpatient attendance in patients with NIIPPU.

Research Question and Objectives

This study aimed to evaluate real life effectiveness of adalimumab (Humira®) in patients with active NIIPPU despite high-dose corticosteroid therapy; including effect on ocular inflammation, health-related quality of life, work ability, health-resource utilization and medication burden. In addition, its purpose was to describe the characteristics of NIIPPU patients treated with adalimumab (Humira®) in the real-life setting.

The primary objective of the study was to evaluate the impact of adalimumab (Humira®) treatment on achievement of treatment response in active NIPPU patients treated with adalimumab (Humira®) during follow-up period. Treatment response at evaluation visits was defined as quiescence, i.e. no new active chorioretinal inflammatory lesions and having anterior chamber (AC) cell and vitreous haze (VH) grade of ≤0.5+ in both eyes.

The secondary objectives of this observational study were to evaluate:

- the proportion of patients with treatment response (quiescence) at each follow-up visit separately;
- the proportion of patients with maintained response during the follow-up period in total and at each follow-up visit separately;
- the incidence of uveitis flares during the follow-up period;
- the changes in retinal thickness during the follow-up;
- the effect of adalimumab (Humira®) on visual acuity;
- the effect of adalimumab (Humira®) on intraocular pressure;
- the effect on workability as measured by Work Productivity and Activity Impairment - Uveitis (WPAI-UV) score and its sub-scores

(% Presenteeism, % Absenteeism, % Total work productivity impairment, % Total activity impairment) during follow-up;

- the effect of treatment on health care resource utilization (cumulative hospital admis-sions, emergency room admissions, outpatient visits and hospitalization).

The endpoints of this study were:

1. Primary endpoint: the proportion of patients with treatment response at any of the follow up visits at 3, 6, 9 or 12 months.

- Definition of response: "quiescence" defined as patients with no new active chorioretinal inflammatory lesions and having AC cell and VH grade of ≤0.5+ in both eyes.

  E.g. achieving quiescence at month 3 and being in state of non-quiescence at months 6, 9 and 12 should be counted as a treatment response as per primary endpoint.

2. Secondary endpoints:

- Proportion of patients with treatment response separately for each follow-up visit. Definition of response: "quiescence" defined as patients with no new active inflammatory lesions and having AC cell and VH grade of ≤0.5+ in both eyes.
- Proportion of patients with flare at any of follow-up visit at 3, 6, 9 or 12 months. Definition of flare: new active inflammatory lesions or AC cell grade of ≥2+ or VH grade of ≥2+ at least in one eye.
- Proportion of patients with maintained response separately for each follow-up visit at 6, 9 or 12 months. Definition of maintained response: quiescence achieved at respective prior visit and no flare at current visit (definitions for quiescence and flare defined earlier).
- Proportion of patients with maintained response at any of the follow up visits at 6, 9 or 12 months.
- Changes in components of WPAI-UV score (% Presenteeism, % Absenteeism, % Total work productivity impairment, % Total activity impairment) from baseline.

- Difference between 1-year cumulative hospital admissions, emergency room admissions, outpatient visits and hospitalization days prior to and during adalimumab (Humira®) treatment.
- Change of CRT from baseline (left eye, right eye).
- Change in BCVA from baseline (left eye, right eye).
- Change in intraocular pressure from baseline (left eye, right eye)

Study Design

This study was performed in a prospective, open label, multicenter, multi-country, post marketing observational cohort setting and was conducted in 12 countries and 24 sites.

The study population consisted of adult patients (aged ≥ 18 years) with diagnosed active NIIPPU who have been treated with adalimumab (Humira®) as per locally approved label and prescription guidelines. As this was an observational, non-interventional study, patients' treatments were to be determined solely by the treating physician, which was to precede the decision to offer the patient the opportunity to participate in the study.

The study consisted of 5 visits within a 12-months observational period: one baseline visit (V0) and four follow-up visits performed at approximately 3-months intervals (V1, V2, V3, V4).

Setting

In this analysis the following countries were included: Austria, Colombia, Czech Republic, Germany, Greece, Hungary, Ireland, Israel, Kuwait, Lebanon, Switzerland, United Arab Emirates

Subjects and Study Size, Including Dropouts

In total, 155 patients were enrolled in the study. 149 of these patients fulfilled all selection criteria and had data for at least one follow-up visit. Thus, these patients were included in the full analysis set (FAS). The COMPLETER analysis set consists of 106 of the FAS patients who completed all visits with no discontinuation of adalimumab (Humira®) during the study.

Variables and Data Sources

Data were to be documented in the electronic data recording form (eDRF). The patient's condition was assessed using the following questionnaires: VFQ-25, WPAI-UV.

Results

Patient disposition

155 patients from 12 countries were included, located in Europe, South America, and the Middle East. 149 of these were included in the full analysis set (FAS). 106 patients completed all visits and continued adalimumab (Humira®) treatment throughout. Mean patient age was 42.3 (range 18-80); with a higher percentage of female patients (62.4%). The majority of the patients' race was classified as Caucasian (80.5%). The majority of patients were working for payment (59.7%), almost a quarter of the FAS population was unemployed or a homemaker (24.8%). Current or former occupations were mainly non-manual jobs (62.4%).

Baseline characteristics

History of NIPPU

Most patients had been diagnosed with NIIPPU more than three years (40.35 months) before study inclusion. Of note, prior NIIPPU duration varied considerably between patients. After first onset of symptoms, it took on average 4.5 months until NIIPPU diagnosis was made, and another 2.5 months (7 months after symptom onset) until treatment was initiated. After the first ophthalmological visit for management of uveitis, it took on average 3 months until a non-ophthalmologist visit took place for additional evaluation of uveitis.

Etiology

In most patients, the etiology of NIIPPU was idiopathic (50.5%), followed by Behçet's disease (16.8%). In the majority of patients (79.9%) both eyes were affected by NIIPPU. Panuveitis was the most frequently given anatomical NIIPPU type (43.0%) followed by intermediate uveitis (30.2%) and posterior uveitis (30.2%). Patients had experienced on average 2.2 flares in the 12 months prior to study inclusion. Importantly, the majority of patients had also experienced prior ocular complications (64.4%), the most frequent complication being macular edema (41.6%) and cystoid macular edema (32.2%). Even more patients reported ocular complications at the time of study inclusion (79.9%).

Effectiveness results

The primary endpoint, i.e. achievement of quiescence at least at one of the follow-up visits, was reached by 91.5% of the FAS patients. In the course of the study, the rate of patients reaching quiescence increased until V2 (approximately 6 months into treatment with adalimumab (Humira®)), and remained then largely stable.

17.2% of the FAS patients had a flare at V1. For V2 to V4 percentages of patients with a flare ranged between 14.8% (V2) and 10.2% (V4). Sustained maintained response, defined as quiescence at all prior visits and no current flare, was documented for 63.1% of the FAS patients at V2, 59.7% at V3 and 56.2% at V4. Thus, at V4, more than half of all patients (who attended V4) showed sustained treatment response throughout the study.

Effective treatment was reflected by a marked decrease in cumulative health care visits over one year, with an average decrease by 8.4 health care visits after study inclusion compared to the prior 12 months. In accordance, workability parameters assessed by WPAI score, improved in all categories. Similarly, the patients' assessment of their functional visual status, evaluated by VFQ-25, improved in the overall score, and in all subcategories during the observational period.

Central retinal thickness decreased markedly by end of the study. Mean intraocular pressure remained also well-controlled and within normal limits throughout the study. Best Corrected Visual Acuity (BCVA) remained largely stable (mean worsening from logMAR 0.7 at V0 to logMAR of 0.8 at V4).

Safety results

In this study, only serious adverse events (SAEs) and adverse events of special interests (AESI; i.e. malignancy in patients of 30 years of age or younger at the time of diagnosis), pregnancies and product complaints were collected.

Overall, 21 SAEs were reported, which occurred in 13 patients. The most frequent SOC was Infections and infestations (4 affected patients; 2.7%), followed by Eye disorders (3 affected patients; 2.0%) and pregnancy, puerperium and perinatal conditions (3 affected patients; 2.0%). All pregnant patients discontinued adalimumab (Humira®).

4 SAEs were assessed as having a possible causal relationship with the intake of adalimumab (Humira®) (SADRs), namely hypersensitivity, atypical pneumonia, sepsis, and drug intolerance (preferred terms according to MedDRA). All SADRs were resolved by end of the study. Overall, no new safety signals were identified.

Discussion

Study results yield a comprehensive and detailed picture of the demographic characteristics of an international patient population diagnosed with NIIPPU under treatment with adalimumab (Humira®). Demographic characteristics were largely in line with known epidemiologic data.

With respect to prior treatment management in the patients' past, the relatively long time between first diagnosis of NIIPPU and the treatment initiation (2.5 months) was striking. Reasons may include the fact that upon presentation at the doctor's office, there were no acute signs of disease activity and thus no need for treatment. However, other reasons may include lack of ophthalmologists' awareness of suitable treatment modalities for NIIPPU.

Overall, patients appeared to benefit from treatment with adalimumab (Humira®), as many patients achieved quiescence over a sustained time, many during the entire study duration of 12 months. More than half of the patients who attended the last visit experienced the strictest effectiveness criterion until V4, i.e. sustained maintained treatment response. As in every observational study, patient attrition throughout the study must be taken into account. Throughout the study, only 21 patients were lost by V4. This relatively moderate loss of patients still allows for pre-/post-treatment comparisons. The beneficial treatment outcomes were also reflected in other ocular findings as well as questionnaire outcomes on workability (WPAI), visual functional status (VFQ-25), and health resource utilization (HRU).

Marketing Authorisation Holder(s)

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