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Long-term Efficacy and Safety of Maintenance Versus Intermittent Infliximab Therapy for Moderate-to-Severe Plaque-Type Psoriasis: the RESTORE2 Trial

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ABSTRACT

BACKGROUND: Infliximab (IFX) is indicated for the treatment of plaque-type psoriasis, but the efficacy and safety of maintenance vs intermittent therapy are unknown.

OBJECTIVE: To assess the long-term efficacy and safety of maintenance vs intermittent therapy with IFX 5 mg/kg in adults with moderate-to-severe, plaque-type psoriasis.

METHODS: This was an extension of the 26-week phase IIIb RESTORE1 trial. Patients who had been randomized to IFX in RESTORE1 and had achieved ≥75% improvement in PASI (PASI75) by the end of that study were randomized to IFX 5 mg/kg as maintenance (infusions every 8 weeks) or intermittent therapy. Intermittent therapy was initiated upon relapse (improvement in PASI from original baseline reduced by >50%). These subjects received no further treatment until they relapsed again.

RESULTS: 441 subjects were randomized 1:1 to maintenance (n=222) or intermittent (n=219) therapy. The study was terminated early due to serious infusion reactions in some intermittent-therapy patients. Consequently, no formal efficacy analysis was conducted, and efficacy variables were summarized by descriptive statistics. PASI50, PASI75, and PASI90 showed that maintenance therapy achieved greater response rates at most time points compared with intermittent therapy. At week 116,* PASI50 response rate was 95% vs 63%, PASI75 was 78% vs 20%, and PASI90 was 48% vs 9% in the maintenance and intermittent groups, respectively.

Overall, the incidence of adverse events (AEs) was comparable between the groups, except for differing numbers of serious infections (8 [4%] maintenance group, 4 [2%] intermittent group) and serious infusion-related reactions (8 [4%] intermittent group, 1 [≤1%] maintenance group). All but one of these acute reactions occurred during the second infusion of an induction cycle. Two deaths occurred in the intermittent group (lung cancer, myocardial infarction) but were deemed unrelated to treatment.

CONCLUSIONS: These limited data might suggest that maintenance with IFX is more efficacious than intermittent therapy in patients with moderate-to-severe, plaque-type psoriasis. Maintenance treatment was well tolerated, with no new safety signals. In the intermittent-therapy arm, we observed an increased incidence of serious infusion-related reactions during the re-induction phase. However, other AEs observed in this group were consistent with the known IFX safety profile.

*These PASI response rates were at week 68, and "week 116" here represents a typographical error.

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INTRODUCTION*

- **Known:** Maintenance therapy with infliximab 5 mg/kg every 8 weeks is an effective treatment regimen in patients with moderate-to-severe, plaque-type psoriasis.[1-3]
- **Unknown:** Is intermittent reinduction therapy, defined as repeated cycles of up to 4 infusions of infliximab 5 mg/kg administered as needed when psoriasis worsens, an effective treatment alternative?
- **Primary objective:** To assess the long-term efficacy of maintenance therapy versus intermittent therapy with infliximab 5 mg/kg.
- **Secondary objective:** To assess the long-term safety of maintenance therapy versus intermittent therapy with infliximab 5 mg/kg.

*Note: See acronym list at end of poster.

METHODS

- Extension of phase IIIb, 26-week RESTORE1 trial (N=868)—a randomized, multicenter, open-label study that compared the efficacy and safety of infliximab versus MTX in adults with moderate-to-severe, plaque-type psoriasis.[4]
- RESTORE2 was a phase IIIb/IV, 128-week study that aimed to compare the efficacy and safety of infliximab maintenance treatment versus intermittent treatment in adults with moderate-to-severe, plaque-type psoriasis.

SUBJECTS

- **RESTORE1:** *Inclusion*—diagnosis of moderate-to-severe plaque psoriasis for ≥6 months prior to screening; candidate for phototherapy or systemic treatment of psoriasis; at least 10% of total body surface area affected by psoriasis; Psoriasis Area and Severity Index (PASI) score ≥12. *Exclusion*—previous treatment with methotrexate (MTX), infliximab, or any other TNF antagonist.
- **RESTORE2:** *Inclusion*—completed the 26 weeks of RESTORE1 (which included 22 weeks of treatment with infliximab), and PASI score improved ≥75% from baseline to week 26. *Exclusion*—RESTORE1 subjects who were randomized to MTX or received MTX at any time during that study.
  - **Baseline evaluations:** Evaluations performed at week 26 in RESTORE1 were used as baseline for RESTORE2.

RESTORE2 STUDY DESIGN

- Eligible subjects were randomized in a 1:1 ratio to
  - **Maintenance therapy:** Subjects received infusion of infliximab 5 mg/kg every 8 weeks (first infusion at week 4/visit 2).
  - **Intermittent therapy:** Subjects received infusion of infliximab 5 mg/kg when week 26 improvement in PASI from original (RESTORE1) baseline was reduced by >50%. Additional infusions possible at 2, 6, and 14 weeks after first infusion (maximum 4/cycle) until response (**Figure 1**).
    - Response defined as ≥75% improvement in PASI from original (RESTORE1) baseline.
    - No further treatment given until another relapse (week 26 improvement in PASI from original baseline reduced by >50%), at which point treatment cycle re-initiated.
    - Intermittent-treatment cycles repeated throughout study whenever subjects relapsed.
- Intermittent-treatment subjects maintained 8-week visit interval, beginning with last infusion of cycle, and completed the same assessments as maintenance-treatment subjects.
- Week 110 was the last at which an intermittent-therapy cycle could begin, to allow 4 infusions (if needed) plus 4 weeks of follow-up.
- Study terminated early due to new safety information (**see safety section under "Results"**).
- Due to early termination, no formal analyses of efficacy were performed (**see "Summary of Statistical Methods" box**). Results should be interpreted with caution.

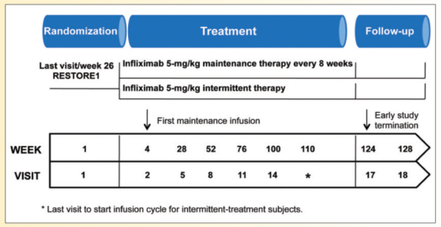

FIGURE 1. RESTORE2 study design.

Summary of Statistical Methods

- Due to early study termination, all efficacy variables summarized by descriptive statistics using the all-randomized data set.
- PASI response rates and change in PASI score from original baseline summarized based on best (minimum) and worst (maximum) and on mean PASI scores for each subject per weekly period.
- Time-adjusted average PASI score summarized using 6- and 12-month AUC.
- Proportion of subjects who achieved PGA of clear or excellent summarized based on best (minimum) and worst (maximum) scores for each subject per weekly period.
- Time-adjusted average PGA score summarized using 6- and 12-month AUC.

INTENDED END POINTS

- **Primary end point:** PASI 75 response rate at week 128. Subjects who dropped out early or had missing data were considered nonresponders.
- **Major secondary end points:** PASI 75 response rate at weeks 52 and 100 and time-adjusted average PASI score over the treatment period.
- **Other secondary end points**
  - Number of infusions, maintenance versus intermittent arm
  - At weeks 52, 100, and 128

    PASI 50 response
    PASI 90 response
    PASI change from baseline*
    DLQI change from baseline*
    Proportion of subjects with PGA of clear or excellent
    SF-36 physical/mental component summary score change from baseline*

    *Change from original RESTORE1 baseline.
- **Exploratory analyses**
  - RADAI change from baseline at weeks 52, 100, and 128
  - EQ-5D change from baseline at weeks 52, 100, and 128
  - Intermittent group—time to first re-induction, number of treatment cycles and infusions per cycle
- **Safety:** Patients monitored throughout study.

RESULTS

- 441 subjects were randomized to maintenance therapy (n=222) or intermittent therapy (n=219; **Table 1**).
- Study terminated early because of safety issues in intermittent arm: No subjects completed treatment phase (**Table 2**).
- Because of early termination, not all intended end points were analyzed (ie, RADAI, EQ-5D, and PGA data).
- **Primary and major secondary end points:** Descriptive summaries demonstrated that maintenance therapy achieved greater PASI 75 response and more improvement in PASI scores at each time point compared with intermittent therapy (**Figures 2, 3**).
- **PASI 50 and PASI 90:** Descriptive summaries favored maintenance over intermittent therapy (**Figures 4, 5**).
- **SF-36:** Mean (SE) changes from original RESTORE1 baseline at weeks 52 and 100, respectively
  - *Maintenance therapy*
    - Physical component summary: 4.04 (0.91), 6.67 (2.10)
    - Mental component summary: 5.71 (1.19), 8.36 (3.09)
  - *Intermittent therapy*
    - Physical component summary: 2.27 (1.17), 0.78 (4.18)
    - Mental component summary: 2.60 (1.46), -0.72 (2.75)
- **Safety:** Early termination of study due to 9 serious acute infusion reactions, 8 in intermittent group and one in maintenance group, from August 24, 2007, to August 23, 2008. All but one of infusion reactions in intermittent group occurred during second infusion of reinduction cycle (approximately 2 weeks after first infusion).
  - *Treatment-related adverse events (AEs)*
    - Most common were nasopharyngitis and infusion-related reactions (**Table 3**).
    - Severe treatment-related AEs occurred in 3% of maintenance subjects (6/222) versus 9% of intermittent subjects (20/219).
    - Of severe AEs, only infusion-related reactions occurred in >1% of either treatment group.
    - No subjects experienced life-threatening AEs considered by investigators to be possibly or probably related to study treatment.

TABLE 1. RESTORE2 Patient Demographics

Characteristics	Maintenance n=222	Intermittent n=219	Total n=441
Gender, male; n (%)	152 (68%)	156 (71%)	308 (70%)
Race, Caucasian; n (%)	218 (98%)	212 (97%)	430 (98%)
Age, years; median (range)	45.0 (18–72)	42.0 (20–72)	44.0 (18–72)
Weight, kg; mean (SD)	85.72 (18.30)	86.50 (19.29)	86.11 (18.78)
Height, cm; mean (SD)	173.65 (9.48)	174.54 (8.74)	174.10 (9.12)
Years since diagnosis, mean (SD)	20.5 (12.0)	17.5 (11.0)	19.0 (11.6)
PASI scores, mean (SD) RESTORE1 baseline RESTORE2 baseline (week 26 of RESTORE1)	21.5 (8.7) 1.7 (1.9)	21.2 (7.7) 1.8 (2.7)	21.4 (8.2) 1.7 (2.3)
Total DLQI scores, mean (SD) RESTORE1 baseline RESTORE2 baseline (week 26 of RESTORE1)	13.7 (6.9), n=218 1.7 (2.6), n=209	14.2 (7.1), n=215 1.9 (3.7), n=210	13.9 (7.0), n=433 1.8 (3.2), n=419

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

TABLE 2. Disposition of Subjects

Subject Disposition	Maintenance n=222 (%)	Intermittent n=219 (%)	Total n=441 (%)
Randomized	222 (100)	219 (100)	441 (100)
Did not receive study medication	5 (2)	46 (21)*	51 (11.5)
Discontinued treatment phase**	222 (100)	219 (100)	441 (100)
Adverse events	26 (12)	29 (13)	55 (12)
Treatment failure	20 (9)	23 (11)	43 (10)
Protocol-defined clinical event	0	1 (<1)	1 (<1)
Lost to follow-up	4 (2)	5 (2)	9 (2)
Subject chose to discontinue#	13 (6)	24 (11)	37 (8)
Noncompliance	6 (3)	9 (4)	15 (3)
Did not meet protocol eligibility	0	3 (1)	3 (1)
Early study termination	153 (69)	125 (57)	278 (63)
Completed treatment phase	0	0	0

*46 subjects (21%) in intermittent-treatment group never experienced relapse. Per protocol, they did not receive study drug cycle.
**Subjects who discontinued treatment were followed for safety by completing evaluations at remaining visits scheduled to occur at 6-month intervals (weeks 28, 52, 76, 100, 128).
#Reasons unrelated to assigned study treatment.

TABLE 3. Summary of Treatment-Related Adverse Events*

Category	Maintenance n=222 (%)	Intermittent n=219 (%)
Subjects reporting any treatment-related AE	86 (39)	83 (38)
Gastrointestinal disorders Diarrhea	7 (3) 3 (1)	9 (4) 4 (2)
General disorders Fatigue Infusion-related reactions	29 (13) 4 (2) 21 (9)	33 (15) 1 (<1) 32 (15)
Infections Influenza Nasopharyngitis	43 (19) 4 (2) 22 (10)	33 (15) 2 (1) 14 (6)
Musculoskeletal and connective tissue disorders Arthralgia	20 (9) 10 (5)	24 (11) 14 (6)
Nervous system disorders Headache	6 (3) 3 (1)	9 (4) 6 (3)
Respiratory, thoracic, and mediastinal disorders Oropharyngeal pain	14 (6) 8 (4)	5 (2) 1 (<1)
Skin and subcutaneous tissue disorders Pruritus Psoriasis	9 (4) 2 (1) 3 (1)	13 (6) 5 (2) 4 (2)
Severe treatment-related AEs All Infusion reactions#	7 (3)** 3 (1)	20 (9)** 11 (5)

*Majority were mild or moderate in severity.
**Maintenance group = acute tonsillitis, influenza, arthralgia, psoriasis (all <1%); intermittent group = neutropenia, abdominal pain, infection, nasopharyngitis, dehydration, arthralgia, arthropathy, joint stiffness, joint swelling, acute pre–renal failure, psoriasis (all but psoriasis and arthralgia <1%).
#None were life-threatening.
AE, adverse event.

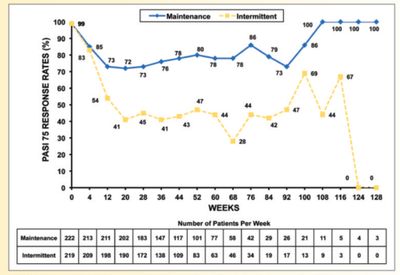

FIGURE 2. PASI 75 response based on best (minimum) PASI score by treatment week (all randomized subjects).

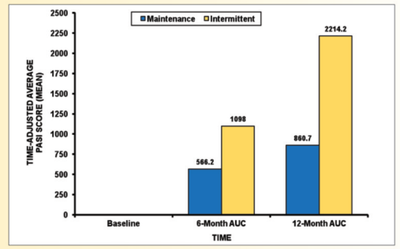

FIGURE 3. Summary of time-adjusted average PASI score (all randomized subjects); AUC, area under the curve.

CONCLUSIONS

- Maintenance therapy with infliximab 5 mg/kg for treatment of patients with moderate-to-severe, plaque-type psoriasis was well tolerated and consistent with known safety profile; confirms results of EXPRESS II trial.[5]
- Intermittent therapy with infliximab was associated with increased incidence of serious infusion-related reactions during reinduction phase (which led to early study termination). Other AEs were consistent with known safety profile.
- Mean change from original RESTORE1 baseline in total DLQI scores (**Figure 6**) and in mean SF-36 scores at weeks 52 and 100 indicated greater improvement in maintenance-therapy group.
- Descriptive data summaries suggest that maintenance therapy with infliximab every 8 weeks is more efficacious in patients with moderate-to-severe, plaque-type psoriasis than intermittent therapy.

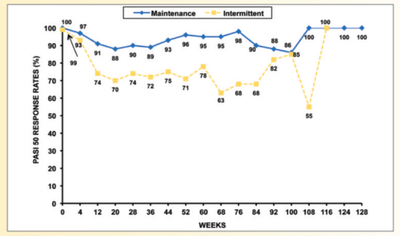

FIGURE 4. PASI 50 response rates based on mean PASI score by week (all randomized subjects). See Patients Per Week box, Fig. 2.

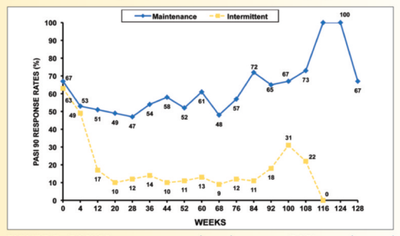

FIGURE 5. PASI 90 response rates based on mean PASI score by week (all randomized subjects). See Patients Per Week box, Fig. 2.

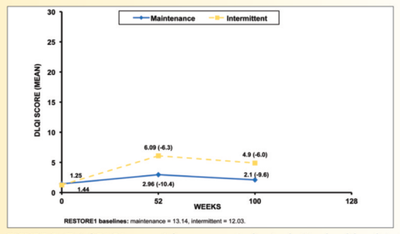

FIGURE 6. Total DLQI score. A lower score indicates better health-related quality of life. Change (in parentheses) is from RESTORE1 baseline. Week 0 baseline of RESTORE2 = week 26 of RESTORE1 DLQI, Dermatology Life Quality Index.

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DISCLOSURES

K Reich has served as a consultant and/or paid speaker for, and/or participated in clinical trials sponsored by, Abbott, Celgene, Centocor, Janssen-Cilag, Leo, Medac, and Merck.

G Wozel has no conflicts of interest to disclose.

H Zheng, H van Hoogstraten, and L Flint are employees of Merck.

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ACRONYMS

AEs, adverse events; AUC, area under the curve; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol Health Questionnaire; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; RADAI, Rheumatoid Arthritis Disease Activity Index; SE, standard error; SF-36, 36-item Short-Form Health Survey.