Utilization of Alternative Dosing Strategies for Infliximab and Infliximab Biosimilars in the Home Infusion Setting

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Background

Presently, there are many biosimilars of infliximab available for various diagnoses compared to when the infliximab reference product, Remicade®, was released in 1998. These medications are approved for the treatment of ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and Crohn's disease.[1] The standard dose for infliximab is 5mg/kg infused over 2 hours at 0, 2, and 6 weeks for induction, followed by every 8 weeks for maintenance. Shortened infusion durations of one hour have been well studied to be safe and effective if patients have tolerated four standard sessions.[2] The loss of response (LOR) to these agents has been well established, with 46% of patients requiring dose escalation within the first year of therapy.[3,4]

Previous studies have established the use of different dosing strategies, including a shortened dosing interval (4 weeks), and doubled-dose (10mg/kg) and found that shortened interval was not superior to doubled-dose in terms of LOR.[5,6] Potential disadvantages of these alternative dosing strategies include an increased risk of serious infections at higher doses and decreased quality of life due to more frequent dosing.[1,6]

Treatment is typically stopped if there is no response by week 14 or if significant infusion reactions have occurred.[1] Acute infusion reactions that are mild to moderate include pruritus, flushing, dyspnea, chest discomfort, hypertension, myalgia, nausea, urticaria, headache, skin rash, and dizziness during the infusion or within 1 to 2 hours of completion.[7] More severe infusion reactions including bronchospasm, angioedema, hypotension, related cardiovascular and cerebrovascular events, and temporary vision loss have also been reported during and following infusion.[8] Delayed infusion reactions, including serum-sickness-like reaction (SSLR) or maculopapular rash, can develop after more than 24 hours, or occur up to 1 to 3 weeks post infusion.[9]

Purpose

The purpose of this study is to compare shortened dosing intervals and doubled-dose with standard dosing of infliximab reference product [Remicade® (infliximab, REM), and infliximab biosimilars Renflexis® (infliximab-abda, REN), Avsola® (infliximab-axxq, AVS), Inflectra® (infliximab-dyyb, IFX)] in order to evaluate the utilization of alternative dosing strategies and compare the tolerability of alternative dosing strategies.

Methods

This was a retrospective, non-randomized, multi-site observational study. Patient data spanning two years was included. Baseline demographics, medication history, dosing strategy, and adverse drug reactions were reviewed. Data was obtained through electronic medical records (EMR). Patients 18 years or older who have previously received or are actively receiving treatment with REM, REN, AVS, and IFX were assessed for shortened interval or doubled-dose strategies. Dose escalation is defined as dose increase or shortened interval, among the dose increase group, the doubled dose population was assessed.

Patients who have been switched between biologics for LOR or treatment failure were also recorded. LOR was measured by worsening symptoms, urgent medical intervention, and discontinuation of the biologic due to infusion symptoms. Patients receiving subcutaneous Zymfentra® (infliximab-dyyb) were excluded from this study. As stated previously, studies have shown the safety and efficacy of rapid infusion. These patients were included whether a patient received a rapid infusion or standard infusion, but this metric was not assessed in this study. This study was determined to be exempt by IRB.

References

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Figure 1: Patient Characteristics

Patient Characteristics (n=202 patients)	Patients (%)
Gender	
Male	79 (39.1%)
Female	23 (60.9%)
Age (range)	
18-27	51 (25.2)
28-37	35 (17.3%)
38-47	41 (20.2%)
48-57	44 (21.8%)
58-67	22 (10.9)
68-77	9 (4.5%)
Frequency of infusions	
Every 4 weeks	18 (8.9%)
Every 5 weeks	2 (1%)
Every 6 weeks	31 (15.3%)
Every 8 weeks	151 (74.8%)
Diagnosis	
Ankylosing spondylitis	4 (2%)
Plaque psoriasis	8 (4%)
Crohn's disease	107 (53%)
Ulcerative colitis	56 (27.7%)
Psoriatic arthritis	1 (0.5%)
Rheumatoid arthritis	18 (8.9%)
Other	8 (4%)
Grand Total	**202**

Figure 3: Reported Adverse Events

Reported Adverse Events (n= 202 patients)	Patients (%)
Acute infusion reactions	
Abdominal pain	2 (1%)
Chest discomfort	43 (21.2)
Diaphoresis	18 (9%)
Diarrhea	3 (1.5%)
Dizziness	17 (8.5%)
Dyspnea	68 (33.7%)
Flushing	79 (39.1%)
Headache	15 (7.4%)
Hypertension	4 (2%)
Nausea	42 (20.8%)
Pharyngitis	12 (5.9%)
Pruritus	35 (17.3%)
Rash	20 (10%)
Tachycardia	9 (4.4%)
Severe infusion reactions	
Anaphylaxis	2 (1%)
Blurry vision	3 (1.5%)
Coughing	17 (8.4%)
Hives	16 (7.9%)
Hypotension	6 (3%)
Numbness	16 (7.9%)
Rigors/Chills	12 (5.9%)
Seizure	1 (0.5%)
Delayed Infusion reactions	
Flu-like symptoms	2 (1%)
Grand total	**202**

Figure 2: Doubled Dose vs Shortened Interval 2022-2024

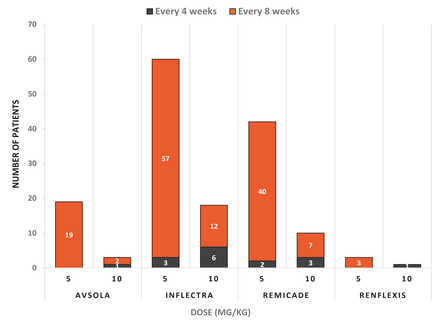
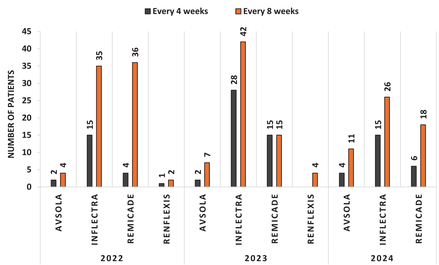


Figure 4: Total Patients with Infliximab Shortened Interval 4 Weeks vs 8 Weeks 2022-2024



Results

A total of 202 patients were included from 92 sites in the United States. In this patient population, ages 18-27 (25.2%) had the most reported adverse drug reactions *(Figure 1)*. Between the two dosing strategies, a total of 59 (29.2%) patients received an increased dose of 7, 8, and 10 mg/kg per dose and 51 (25.2%) patients had shortened interval dosing every 4, 5, and 6 weeks. IFX had both the highest percentage of patients experiencing adverse drug events: doubled dose 19 (9.4%) patients and shortened interval dosing 9 (4.4%) patients receiving 4-week dosing intervals *(Figure 2)*. The most common adverse reactions were flushing, dyspnea, and chest discomfort *(Figure 3)*. Out of 224 reported adverse drug reactions, 171 (76.3%) were managed in the home. Twenty-one (10.4%) patients had previously attempted a different infliximab biosimilar. There were 170 (84.1%) patients who experienced an adverse drug reaction and discontinued infliximab, the 32 patients (15.8%) remaining continued the same therapy. Of patients who discontinued treatment, 91 patients (45%) switched to a different biologic class.

A total of 292 patients were included for frequency change from 8-week to 4-week intervals *(Figure 4)*. From 2022 to 2023, IFX showed the highest percent increase (50%) of patients started on 8-week intervals and converted to 4-week intervals. Sixty percent of total patients in the IFX group were on 4-week intervals in 2023, increasing to 63% of total patients in 2024. The REN group in 2023 had no patients on shortened interval dosing. In 2024, no patients were actively receiving REN. AVS had a gradual shift from 66% of total patients in 2022 to 73% in 2024.

Discussion

Currently, infliximab biosimilars are utilized for several indications related to autoimmune diseases with standardized dosing strategies, however there is minimal data on the guidelines for patients with increased tolerance. After induction, two LOR mitigation strategies were utilized: patients who had doubled dosing utilized (10mg/kg) or patients who had decreased intervals shortened to four weeks. Doses were recorded from the time the adverse drug reaction was reported. Reported events occurred in the home or in an infusion center under observation of a nurse.

Premedication (corticosteroids, antihistamines, and/or antipyretics) was determined at the ordering provider's discretion and the patient was given the option to decline prior to each infusion. Patient weights (kg) were rounded to the nearest whole number and doses were grouped to the nearest 100 mg per prescriber orders. Unrelated to dosing, some patients discontinued an effective agent without any tolerability issues due to insurance coverage.

Conclusion

This study demonstrates the tolerability of the dose escalation group when adjusting for an increased tolerance of the medication. Of 202 patients, 46 (22.8%) patients received double dosing of 10mg/kg. A total of 18 (8.9%) patients received reduced frequency dosing every 4 weeks. The difference in patients who had adverse drug reactions reported was higher in the increase dose population (7, 8, and 10mg/kg) compared to the shortened interval (6, 5, 4 weeks) was 3.8%. The doubled-dose population (10mg/kg) compared to the shortened interval (every 4 weeks) had a difference of 13.9% adverse drug reactions reported. The severity of adverse drug reactions was variable across the patient population. However, the definitive reasoning for prescribing practices has yet to be determined.

This analysis of dose increase and shortened interval provides a baseline trend of how infliximab biosimilars are prescribed. Further studies are needed to provide background on prescriber initiation of therapy related to tolerability risk assessment for indications to determine which patients can receive dose escalation after therapy induction.

Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation: Natalie Garcia; Andrew Chinn; Cara Bivona; Maria Giannakos; Christopher Roy; Michelle Sahlani; David Shepherd: Nothing to disclose.

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