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The Efficacy of Sequential Biologic Agents in Refractory Rheumatoid Arthritis after Failure of Initial DMARD and anti-Tumor Necrosis Factor Therapy

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Abstract: Introduction/Objective: The efficacy of biologic therapy in the treatment of rheumatoid arthritis (RA) has been well-established but, in practice, a quarter of patients will either not respond to the first biologic agent or will suffer an adverse event requiring a switch to a different drug. While clinical guidelines exist to help guide therapy and previous studies have examined sequential use of anti-TNF agents, there is little data to inform a multiple switch strategy. Our aim was to measure the efficacy of multiple switches of biologic in severe refractory RA. Methods: We enrolled 111 patients whose therapy with one anti-TNF agent had failed in this open-label observational study. These patients were all treated with a second biologic agent and 27 ultimately required treatment with a third. The response to the therapy and disease activity were assessed at 6 and 12 months after each switch. Results: The remission rates at 6 months were lower than previously reported and the initiation of a second biologic agent resulted in significant improvement at 12 months, including DAS remission in 36% of patients. The response in those receiving a third biologic was less pronounced, as might be expected in this relatively treatment-refractory population. In this group, only patients treated with tocilizumab had maintained remission at one year. Conclusion: Patients who do not respond to an anti-TNF agent often benefit from being switched to a second, or even third, biologic. Importantly, it may take longer than expected to fully assess the effectiveness of a second or third agent in patients with refractory disease.

Keywords: rheumatoid arthritis; drug treatment; anti-TNF; biologics

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1. Introduction

The treatment of rheumatoid arthritis (RA) has changed greatly in recent years due to the introduction of biologic therapy. These agents specifically target intercellular signaling pathways, co-stimulatory molecules, cytokines, or specific cell populations and can induce a significant therapeutic response, leading to improved signs and symptoms of disease as well as slowing or preventing structural damage [1]. Clinical trials and observational studies have shown that 50–70% of RA patients respond to biological therapy, according to ACR and EULAR criteria [2–8]. However, a significant proportion of patients will fail to respond or have an adverse reaction to their first biologic [9–13] and require a change to an alternative drug. With the recent approval of novel agents with differing mechanisms of action, there are a number of treatment options available after the failure of the first biologic. Previous studies examining the response to therapy in patients being switched from one

agent to another have demonstrated that the efficacy and safety of the second agent is usually comparable, or at least not markedly inferior, to initial anti-tumor necrosis factor (anti-TNF) therapy [14–22]. Most studies to date, however, have only assessed sequential anti-TNF therapy over relatively short time spans. The possibility of employing drugs with different mechanism of actions, such as Il-6 blockade by tocilizumab or CD80/86–CD28 T cell co-stimulation modulator by abatacept, offers the possibility of assessing response rates in comparison to anti-TNF inhibitors. Therefore, the primary aim of our study was to evaluate the response rates up to one year in patients with refractory disease who had already failed to respond to one or two anti-TNF agents and were undergoing switch to a second or third biologic agent.

2. Materials and Methods

This was a non-interventional, open-label, "real-world" observational study. Patients with RA were recruited from January 2015 to December 2019 from the Rheumatology Unit in the Department of Clinical and Experimental Medicine of the University of Messina. All RA patients fulfilled the 2010 ACR classification criteria [23].

In total, 301 biologic agent-naïve RA patients (study population) began initial therapy with an anti-TNF agent. Of these, 111 (women: 80, men: 30; age range: 43–71) subsequently failed to respond to the therapy (defined as persistent clinical symptoms and a DAS28 > 5.1) and were switched to a second biologic. Then, 27 of these patients (women: 22, men: 5; age range: 50–67) failed to respond to therapy with the second agent and were ultimately switched to a third. The choice of agent was not restricted by protocol and was left up to the discretion of the treating rheumatologist. Baseline data, including demographics, disease duration, past and current use of disease-modifying anti-rheumatic drugs (DMARDs), disease activity score in 28 joints (DAS28), and Health Assessment Questionnaire (HAQ) were recorded prior to the initiation of the second or third biologic agent. The outcomes of interest included the EULAR response criteria and proportion of patients achieving low disease activity (DAS28 between 2.85 and 3.2), minimal disease activity (DAS28 between 2.6 and 2.85), and remission (DAS28 < 2.6). Patients not evaluated at 6 months were defined as dropouts and were not included in further analyses. No additional visits or laboratory tests were required outside of routine clinical practice. In total, 62% of patients were on background methotrexate and 20% were on other DMARDs. The initial biologic chosen for all patients was an anti-TNF inhibitor. Patients were followed every 10 weeks, on average, and the goal was the remission of the disease (DAS28 < 2.6). In the majority of patients receiving a second agent, anti-TNF therapy (infliximab, etanercept, adalimumab) was used (54%) while abatacept (n = 24) and tocilizumab (n = 27) accounted for the remainder. Treatment doses were: infliximab 3 mg/kg every 8 weeks iv; adalimumab 40 mg every 2 weeks sc; etanercept 50 mg every week sc; abatacept 10 mg/kg every 4 weeks iv; tocilizumab 8 mg/kg every 4 weeks iv. This study was approved by the ethics committee of the Faculty of Medicine at the University of Messina (98–15). All patients provided their written informed consent.

Results are expressed as mean values ± standard deviation or percentage. Student's t-test was used in the between-group analysis and p values < 0.05 were considered statistically significant.

3. Results

During the study period, 301 patients were initiated with a first biologic agent. Of these, 163 patients either responded well and did not require a switch to another biologic or they experienced an adverse event precluding the use of another biologic agent. Of the 138 patients who then received a second biologic, 27 could not be evaluated at 6 months and were not assessed further due to treatment discontinuation or follow-up delay. The remaining 111 patients were subsequently switched to a second agent (group I) and 36 of these were ultimately switched to a third (group II), with 9 patients lost to follow-up due to treatment discontinuation or follow-up delay (Figure 1). The reasons for the switch

to a different biologic therapy in group I was inefficacy. In group II, the reasons for the switch to a different biologic agent were inefficacy in 93% and serious infection in 7% of the cases. No neoplasms or autoimmune disorders were observed during the study period. There were no significant differences in the baseline demographics between the two groups, except for a longer duration of the disease in group II (Table 1). Both groups of patients had initially failed to respond to treatment with anti-TNF therapy (adalimumab, infliximab, etanercept). The overall response rates, according to EULAR criteria, are shown in Table 2. At 6 months, the response rate in those undergoing the first switch in therapy was "moderate" in 81% and "good" in 8% of patients, and in those then switched to a third agent (group II) response rates were 26% and 22%, respectively. At 12 months, 33% of group I and 77% of group II had a "moderate" response. At 12 months, the rate of "good" response was lower in those undergoing the second switch as compared to those undergoing the first (23% versus 67%). Based on DAS28 at 6 months, 10% of patients from group I and no patients from group II were in remission. At 12 months, 32% of patients in group I had low disease activity and 36% were in remission, while in group II, 11% were in remission and 11% had low disease activity (Figure 2A).

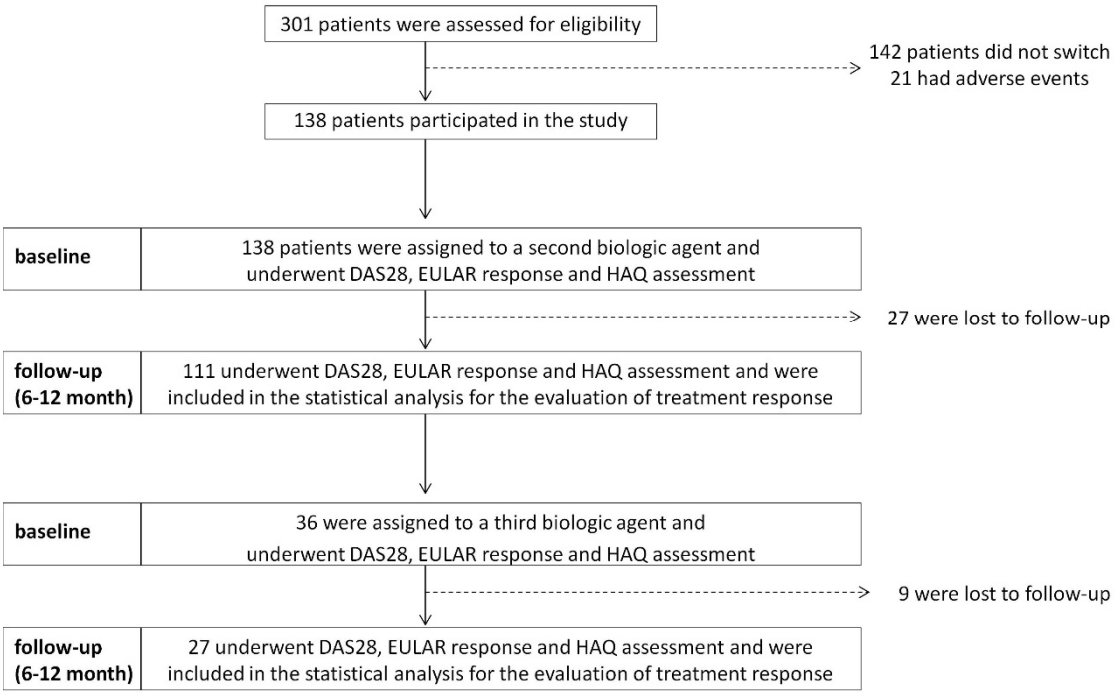

Figure 1. Patient flow chart showing the number of patients (n = 301) evaluated for eligibility and subsequently enrolled in the study (138). Patients who failed to respond to therapy with the initial anti-tumor necrosis factor α were switched to a second biologic (n = 138) and evaluated through DAS28 and EULAR response criteria for disease activity and through HAQ for functional status after 6 and 12 months. Patients that switched to a second biologic and failed to respond to therapy were then switched to a third biologic (n = 36) and evaluated according to the outcome measurements used for the first switch. DAS28, Disease Activity Score 28 joints; EULAR, European League against Rheumatism; HAQ, Health Assessment Questionnaire; RA, Rheumatoid Arthritis.

3.1. Drug-Specific Response Rates and Disease Activity-Group I

At the 6-month follow-up, all drugs produced at least a "moderate" response in more than half of patients in group I. The rates of "good" response ranged from 0% for tocilizumab and infliximab to 25% for adalimumab (Table 2). At 12 months, the percentage of patients achieving a "good" response rose for all drugs, including a rate of 100% for infliximab. By 6 months, disease remission was achieved with 3 agents, abatacept (12.5%), adalimumab (25%), and etanercept (9%), while at 12 months, the remission rate ranged from 25% to 60% for all drugs (Figure 2C–G).

Table 1. Baseline characteristics of patients included in analyses. * $p < 0.001$.

	First Switch (Group I)	Second Switch (Group II)
Age (y), (mean ± SD)	54 ± 8.47	53 ± 7.93
BMI (Kg/m^2), (mean ± SD)	25.02 ± 4.04	25.14 ± 4.99
Female (%)	89 (80)	22 (82)
Duration of disease (y), (mean ± SD) *	13.37 ± 6.12	27 ± 7.56
DAS28, (mean ± SD)	5.63 ± 1.30	5.33 ± 2.19
HAQ, (mean ± SD)	2.07 ± 0.50	1.94 ± 0.67
Concurrent corticosteroid use		
None, *n* (%)	22 (20)	5 (19)
≤5 mg, *n* (%)	67 (60)	15 (56)
>5 mg, *n* (%)	15 (18)	6 (22)
Concurrent MTX use, *n* (%)	69 (62)	16 (60)
Weekly MTX dose (mg), (mean ± SD)	8.80 ± 2.40	9.2 ± 2.20
Concurrent other DMARDs use, *n* (%)	22 (20)	6 (22)

Table 2. Drug-specific EULAR response in both study groups. According to the EULAR criteria, the response rates have been classified as no response, moderate and good response based on the changes in the disease activity score in 28 joints at 6 and 12 months.

	First Switch (Group I)		Second Switch (Group II)	
	6 Months	**12 Months**	**6 Months**	**12 Months**
	Tocilizumab (*n* = 24)		Tocilizumab (*n* = 6)	
No response, *n* (%)	3 (12.5)	0 (0)	0 (0)	0 (0)
Moderate response, *n* (%)	21 (87.5)	6 (25)	3 (50)	3 (50)
Good response, *n* (%)	0 (0)	18 (75)	3 (50)	3 (50)
	Abatacept (*n* = 24)		Abatacept (*n* = 9)	
No response, *n* (%)	6 (25)	0 (0)	3 (33)	0 (0)
Moderate response, *n* (%)	15 (62.5)	18 (75)	3 (33)	9 (100)
Good response, *n* (%)	3 (12.5)	6 (25)	3 (33)	0 (0)
	Adalimumab (*n* = 12)		Adalimumab (*n* = 3)	
No response, *n* (%)	0 (0)	0 (0)	2 (66)	0 (0)
Moderate response, *n* (%)	9 (75)	6 (50)	1 (33)	3 (100)
Good response, *n* (%)	3 (25)	6 (50)	0 (0)	0 (0)
	Etanercept (*n* = 33)		Etanercept (*n* = 9)	
No response, *n* (%)	0 (0)	0 (0)	9 (100)	0 (0)
Moderate response, *n* (%)	30 (91)	6 (18)	0 (0)	6 (66)
Good response, *n* (%)	3 (9)	27 (82)	0 (0)	3 (33)
	Infliximab (*n* = 15)			
No response, *n* (%)	0 (0)	0 (0)		
Moderate response, *n* (%)	15 (100)	0 (0)		
Good response, *n* (%)	0 (0)	15 (100)		

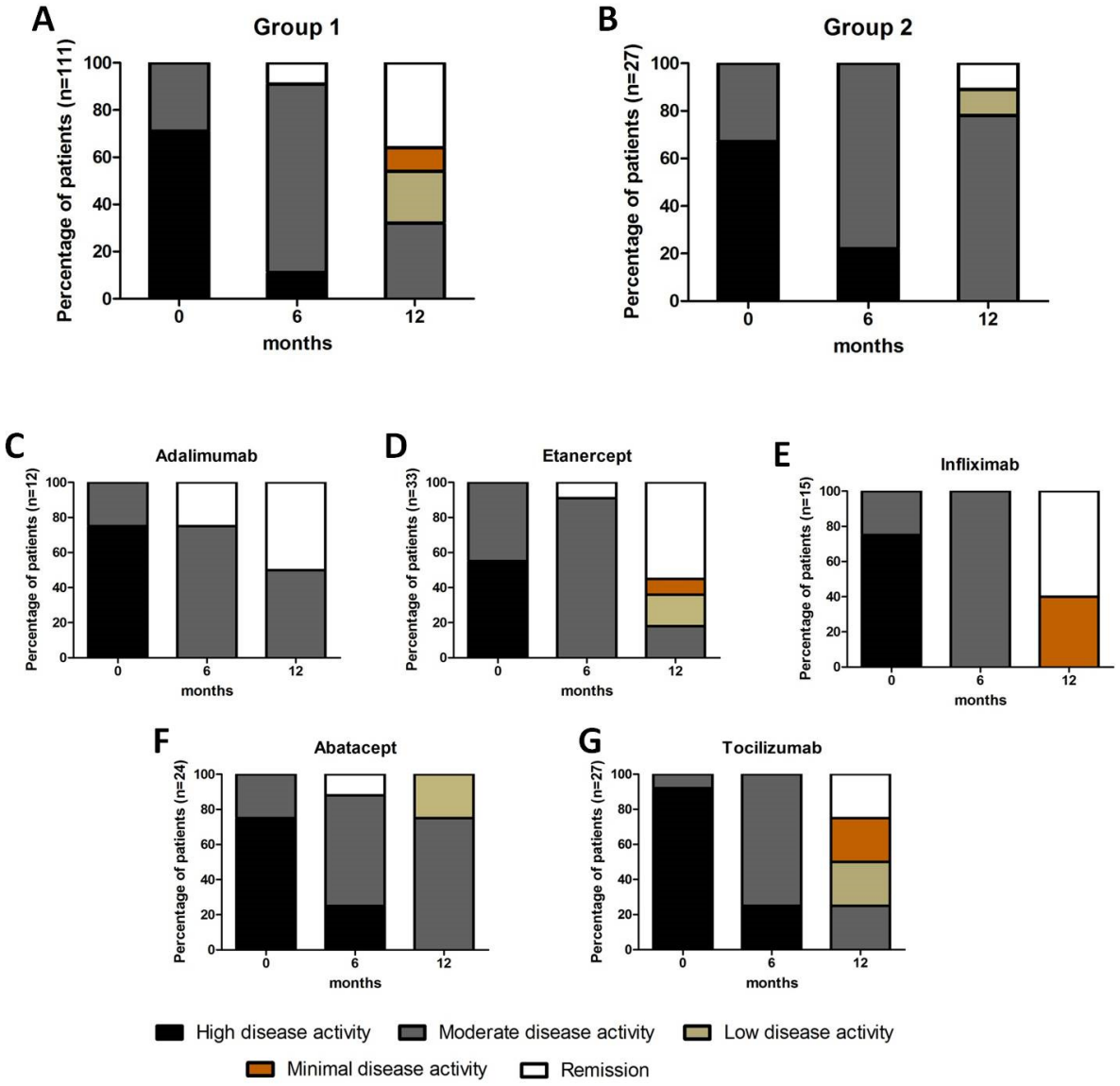

Figure 2. (**A**–**G**). DAS28 changes over time, classified in high disease activity (DAS28 > 5.1), moderate disease activity (DAS28 between 3.2 and 5.1), low disease activity (DAS28 between 2.85 and 3.2), minimal disease activity (DAS28 between 2.6 and 2.85) and remission (DAS28 < 2.6), for RA patients that switched to a second biologic (group I) and for RA patients that switched to a third biologic (group II). (**A**) In RA patients that switched to a second biologic (n = 111), DAS28 at baseline was high for 79 and moderate in 32 patients, while after 1 year of treatment, disease remission was obtained in 39, no patients had a high disease activity and the remaining had a disease activity between moderate and minimal. (**B**) Although the numbers of patients affected by refractory RA that switched to a third biologic were low (n = 27), 18 patients had a high baseline disease activity and 9 had a moderate disease activity. After 1 year, there were no patients with high disease activity, 21 had a moderate disease and 3 reached disease remission. (**C**–**G**) The subsequent analysis was performed to compare the efficacy of different biologic agents in RA patients that switched after the first biologic failure. (**C**) Among patients treated with tocilizumab (n = 24), almost all of them (n = 22) had a high disease activity and the improvement in DAS28 was evident at 6 months, with 6 patients having high disease activity. In 1 year, 6 patients reached remission, while no patients had high disease activity. (**D**) For Infliximab (n = 15), after 6 months patients improved and were all in moderate disease activity and in 1 year, 9 were in remission and 6 had a minimal disease activity. (**E**) Among patients treated with abatacept (n = 24), the remission obtained at 6 months in 3 patients was not sustained at 1 year and patients were all between low to moderate disease activity. (**F**) Adalimumab (n = 15), as a second agent, was effective in inducing remission in 3 patients at 6 months and 6 patients in 1 year of treatment. (**G**) Remission was observed in 3 patients among those switched to etanercept (33) at 6 months and in 18 after 1 year of therapy. Drug-specific analysis suggests that 6 months is not enough time to evaluate the response of patients who switch to a second biologic agent.

3.2. Drug-Specific Response Rates and Disease Activity-Group II

At 6 months, tocilizumab and abatacept produced a EULAR response of "good" in group II in 3/6 and 3/9 patients, respectively. No other agent produced a "good" response. At 12 months, 3/6 patients on tocilizumab and 3/9 of those on etanercept maintained a "good" response, while those switched to adalimumab and abatacept only reached a "moderate" response (Table 2). At the 6-month follow-up, 3/6 and 3/9 patients treated with tocilizumab and abatacept were in remission, while at 12 months, only patients treated with tocilizumab remained in remission. The DAS28 changes over time for group II are shown in Figure 2B. However, the numbers were too small for statistical or graphical analysis.

Overall, functional status as assessed by HAQ scores significantly improved in both groups at 6 and 12 months of follow-up (Table 3). In group I, infliximab, adalimumab, and etanercept produced a HAQ < 0.5 at 12 months, while in group II, only tocilizumab elicited this response.

Table 3. HAQ at baseline and at the 6- and 12-month assessment. Values are expressed as the mean ± SD. * $p < 0.0001$.

	Group I (*n* = 111)	**Group II (*n* = 27)**
HAQ_0	2.07 (0.51)	1.94 (0.47)
HAQ_6	0.98 (0.37) *	1.01 (0.46) *
HAQ_{12}	0.53 (0.18) *	0.78 (0.37) *

4. Discussion

It is well-established that the aggressive treatment of early RA with the goal of low-disease activity can produce higher rates of disease remission and less joint damage and deterioration. Clinical guidelines have been published to aid practitioners in choosing which initial agents to use in a given patient, and when to change therapy when the desired outcome has not been achieved. In general, however, recommendations regarding changing from one biologic to another rely on expert consensus opinion [24–26] and there is even less data available to guide the management of patients who have failed to respond to multiple biologic agents.

This study confirms that patients who failed to respond to the initial biologic therapy with an anti-TNF agent may obtain a significantly beneficial response after switching to a second, or even third, drug. Overall rates of "moderate" and "good" EULAR responses in both groups of patients were consistent with previous studies. However, remission rates at 6 months in those patients undergoing the first switch was lower than had been previously reported [27,28]. Karlsson et al.; for example, reported an overall remission rate of 16% in patients undergoing the first switch at 3 months [29]. This discrepancy may be explained by the unequal follow-up period between the two studies and, in fact, we found remission rates of 36% in group I and 11% in group II at 12 months. In addition, all drugs (except for abatacept) showed significantly higher rates of remission compared to the baseline in both groups. This may suggest either regression to the mean, or that 6 months may not be enough time to fully assess the capacity of a biologic agent to induce remission in this relatively treatment-refractory population and that remission may still be possible even in patients who have failed to respond to multiple biologic agents, particularly when a drug with a different mechanism of action is used.

While the EULAR response was similar at 12 months in all patients across all biologic agents, we did note drug-specific differences in disease activity. In those undergoing the first switch in therapy (group I), the highest rates of remission at 12 months were seen in patients treated with infliximab and etanercept. In those receiving abatacept, none achieved remission and 75% continued to have moderate disease activity. This result is in contrast to recent investigations suggesting that abatacept is specifically effective as a switch therapy in patients who have failed to respond to an anti-TNF agent [30,31].

In general, patients being switched to a third biologic agent would be expected to have more severe disease and diminished response to therapy. This hypothesis was borne out as there were, in fact, lower rates of "good" EULAR response in this population. However, there were no patients who were completely refractory to therapy, as all showed at least a "moderate" response to a third agent. This observation is clinically significant and reinforces current practice. Interestingly, the only biologic able to induce remission in this group at 12 months was tocilizumab, with 50% (3/6) of patients achieving this outcome. This observation is in line with data published by Emery et al.; who demonstrated a 30% remission rate in a phase 3 study of tocilizumab in patients being switched from a previous biologic agent [32]. In contrast, all patients receiving abatacept or adalimumab and two thirds of those treated with etanercept continued to have moderate disease activity.

Indeed, the reasons for discontinuation due to the occurrence of adverse events or inefficacy represents a different background that orientates the choice of a subsequent biologic agent. Thus, in larger RA studies, retention rates should be better stratified to identify factors predisposing to "moderate" to "good" response according to the specific reason for biologic failure.

The strength of this study lies in its "real-world" applicability. No limitations were placed on the choice or sequence of the biologic therapy. The results, therefore, represent a wide range of treatment decisions made in the course of usual patient care. This is simultaneously a limitation since, in an observational study of this kind, it is not possible to control for all confounding factors, which raises the possibility of confounding by indication. The study physicians were free to choose any biologic agent, and disease severity or specific patient factors may have influenced their selection. The baseline disease activity, however, was similar in both patient groups and for each biologic agent, suggesting that disease severity was roughly equal at the time of the therapeutic switch. In addition, the long duration of the therapy for each agent and the lengthy timeframe of observation would be expected to dampen the usual fluctuations in disease activity and the effects of regression to the mean. Dropout rates were relatively high, however, this may not be unexpected in patients with a severe disease that is resistant to multiple agents.

There are relatively few patients in group II, making it impossible to arrive at any definitive conclusions regarding either drug efficacy or the optimal sequence of biologic use. This small cohort, however, represents patients who have failed to respond to numerous agents, including multiple biologics. There is little data to guide the therapy in this group and randomized clinical trials in this patient population would be quite difficult. Our data, while based on low numbers, suggest that changing to a drug with a different mechanism of action is a rational approach and generate the hypothesis that tocilizumab may be a particularly effective third- or fourth-line agent in refractory disease. More data, greater numbers of patients, and a protocolized randomized study would be needed to confirm this.

In summary, we have shown that a switch of therapy to a second or even third biologic agent may be beneficial at 12 months in patients who have failed to respond to previous treatment with an anti-TNF agent, and that a longer time course may be needed to see the full benefit of therapy in this relatively treatment-resistant patient population. In addition, switching to an agent with a different mechanism of action may produce a better clinical response and tocilizumab may merit specific consideration as second- or third-line therapy.

Author Contributions: Conceptualization: A.G.V., G.B.; Methodology: A.G.V., M.C., M.C.T., A.D.G.; Writing: A.G.V., C.O.A., D.L.R., D.S., W.N.R., G.B.; Visualization: C.O.A., M.C.; Validation: C.O.A., D.L.R., A.D.G., C.F.M.J.; Formal analysis: D.L.R., M.C.T., C.F.M.J.; Investigation: M.C., M.C.T., A.D.G., C.F.M.J.; Formal analysis: D.L.R., M.C.T., C.F.M.J.; Supervision: D.S., W.N.R., G.B.; Review and Editing: D.S., W.N.R., G.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee) of the University of Messina (protocol code 98/15–2015).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare they have no conflict of interest.

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