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REVIEW ARTICLE

Is It Possible to Discontinue Tumor Necrosis Factor Antagonists after Psoriasis Remission?

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Tumor necrosis factor (TNF) antagonists are highly effective treatments for psoriasis. These agents provide the opportunity to improve disease activity and achieve clinical remission. Despite its efficacy, long-term use of biologics is associated with high financial costs and possibly life-threatening adverse events. Recently, there has been an increasing interest in discontinuing TNF antagonists in patients with psoriasis who have achieved a positive clinical response. However, there is a paucity of data and clinical guidelines concerning the cessation TNF antagonists in psoriasis treatment. Several factors, including cost, subsequent treatment efficacy, relative risks, and tolerability, should be considered before the decision is made to discontinue TNF antagonists. Well-designed clinical trials are necessary to identify factors that may trigger disease exacerbation after medication discontinuation in order to recognize the potential disadvantages of discontinuing treatment in patients who are previously successfully managed on TNF antagonists.
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-Keywords-
Discontinuation, Psoriasis, Remission, Tumor necrosis factor antagonist, Withdrawal

INTRODUCTION

The primary goal of psoriasis treatment is to achieve clinical remission. The recent discovery of biologic agents, including tumor necrosis factor (TNF) antagonists (adalimumab, infliximab, certolizumab pegol, and etanercept), has increased the likelihood of attaining clinical remission, as these agents have the ability to produce rapid and sustained suppression of psoriasis symptoms with good safety profiles.

Conventional systemic agents used to treat psoriasis have been utilized intermittently because of complications such as toxicity, inconvenience, cost, or other comorbidities[1]. In contrast, TNF antagonists have been allowed for continuous use while maintaining their efficacy and safety[1]. Premature treatment discontinuation may result in disease exacerbation. Nevertheless, there is an ongoing debate on whether patients should continue TNF antagonists after achieving clinical remission, and if so, for how long. Criteria guiding termination or interruption of treatment have not been established, but may be valuable in the clinical setting[2].

Recently, arguments supporting the discontinuation of TNF antagonists in rheumatoid arthritis (RA) patients in clinical remission have gained support[3]. In contrast to RA, patients with psoriasis do not show a progressive course; thus there may be fewer reasons not to consider temporary interruption of TNF antagonists after clinical remission of psoriasis.

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Despite this, discontinuation of TNF antagonists can have several advantages, including reducing financial commitment, possible long-term adverse events, and improved patient satisfaction[3].

The aim of this review is to discuss the possibility of discontinuing TNF antagonists once clinical remission is achieved in psoriasis patients. We examine the efficacy and, safety of common TNF antagonist therapy (etanercept, adalimumab, and infliximab) in psoriasis patients and further evaluate this topic in other chronic inflammatory diseases. Lastly we discuss the possibility for criteria of medication discontinuation.

DISCONTINUATION OF TUMOR NECROSIS FACTOR ANTAGONISTS AFTER REMISSION IN PSORIASIS

Despite the long history of intermittent or rotational therapies for psoriasis, the preponderance of data favors the continuous use of TNF antagonists. Reasons for this include risk of ant-drug antibody formation, continued safety with prolong use and efficacious maintenance of symptom control[1,4-6].

Continuous therapy of TNF antagonists is often advised in order to prevent risk of anti-drug antibody formation. Two studies have described increases in anti-drug antibody development in patients who achieved initial remission but developed secondary symptoms and required re-initiation of TNF inhibitor therapy[7,8]. Moreover, it is well known that decreased efficacy of TNF antagonists correlates with the prevalence of serum anti-drug antibodies (more apparent with infliximab and adalimumab than with etanercept)[9,10].

Additionally, several reports have compared the efficacy of intermittent and continuous psoriasis therapy with TNF antagonists. In a systematic review by Brezinski and Armstrong[7], the efficacy of off-label dosing regimens revealed that discontinuing biologics after remission subsequently increased psoriasis activity. Additionally, the efficacy of retreatment yielded poorer response when compared to initial treatment response[7].

Similarly, Ramirez-Fort et al.[1] speculated continuous treatment was required to suppress inflammatory activity and minimize cutaneous involvement. This data supported the superiority of continuous biologic treatment over intermittent therapy, in terms of improved efficacy and safety[1].

However, recent studies have shown differing results and support the notion that retreatment with TNF antagonists has excellent efficacy for psoriasis. Though absolute efficacy of intermittent therapy may be lower when compared to continuous therapy, there are many reports showing the recovery of initial response upon restarting therapy. Thus, the option of treatment discontinuation in cases of clinical remission can be fully considered. In this review, we focus on the most commonly and successfully used TNF antagonists in psoriasis treatment, etanercept, adalimumab, and infliximab.

Etanercept

The first study to examine etanercept retreatment in patients who discontinued therapy after initial positive response (>50% improvement in the Psoriasis Area Severity Index [PASI]), was published in December 2006. The results suggested that medication discontinuation could be considered without unwanted effects in patients who initially responded well to etanercept. Furthermore, most patients regained good disease control upon retreatment (83% attained at least PASI50 at week 12 of retreatment). The formation of anti-drug antibodies was not an issue in etanercept retreatment[11].

Another clinical trial examining moderate to severe plaque psoriasis demonstrated greater improvements with continuous etanercept therapy in comparison to intermittent therapy: at week 24, response was seen in 71.0% and 59.5% of patients respectively[12]. However, in patients receiving intermittent therapy who experienced relapse in symptoms, most were able to achieve responder status after restarting etanercept[12].

In a patient-reported outcomes study, continuous therapy was favored. However, similar levels of improvement prior to medication discontinuation were seen in retreated patients who were previously on intermittent therapy. With this data, the authors concluded that etanercept interruption was a possible option because the drug produced predictable and manageable effects[13].

In the CRYSTEL study[14], a clinical trial evaluating etanercept in psoriasis patients, the continuous therapy group demonstrated a considerably lower mean Physician's Global Assessment (PGA) score than the paused therapy group at an average of 54 weeks (1.98 vs. 2.51). However, both groups revealed an overall improved PGA and PASI scores and patient satisfaction rates. Additionally, 83% of relapsed patients (PGA >2) in the paused therapy group were able to regain their treatment response after resuming etanercept within a median of 15 weeks[14]. Similar results were seen in the intermittent therapy group in a subset of patients who achieved PGA ≤1 before discontinuation of etanercept[15].

Adalimumab

Unlike etanercept, reports discussing intermittent adalimumab efficacy in psoriasis are limited.

A 2011 multicenter open-label study[16] examined a subgroup of 285 patients with stable psoriasis, defined as maintaining a PGA score of 0 (clear) or 1 (minimal) on adalimumab for greater than 12 weeks before the withdrawal of therapy. The efficacy and safety of adalimumab was evaluated in cases of interrupted treatment with subsequent resumed therapy. A PGA score was assigned before medication withdrawal and patients were monitored for relapse of a PGA score of 3 (moderate) or worse[16]. In 178 patients who relapsed (median time to relapse, 141 days), the rate of achieving clearance (PGA $\leq$1) after adalimumab retreatment was 69%. This study found no difference in safety profile between the interrupted and continuous therapy groups. Minimal (2%) risk of formation of anti-adalimumab antibodies were seen with intermittent therapy. Therefore, the authors concluded that the clinical efficacy of adalimumab often is regained with retreatment after relapse following treatment discontinuation[16].

In 2013, the REVEAL open-label extension study[17], adalimumab retreatment and continuous treatment group demonstrated similar efficacy rates in terms of the PASI75 (75% reduction in PASI severity) response at week 108. Compared with the continuous treatment group, the retreatment cohort had equivalent or lower adverse event rates. However, serum anti-adalimumab antibodies were not measured in this study.

Another analysis by Gordon et al.[18] examined a similar subpopulation of patients, who participated in the 2011 adalimumab open-label extension trial[16,17]. Results were similar to the REVEAL study[17], in regards to efficacy and safety. Additionally, the authors concluded that in addition to improved clinical symptoms, adalimumab retreatment improved patients' health-related quality of life.

Infliximab

In 2007, Menter et al.[5] conducted the first study to directly compare maintenance regimens and intermittent therapy of biologics. They conclude that continuous (every 8-week) use of infliximab at a dose of 5 mg/kg had greater efficacy, defined as maintenance of PASI75 and PASI90 responses in comparison to intermittent as-needed regimens in patients with moderate to severe psoriasis during one year of treatment (54.5% vs. 38.1% for PASI75 and 34.3% vs. 10.4% of PASI90 at week 50)[5]. If the improvement from baseline was less than PASI75, the as-needed maintenance group received the original infliximab dose[5]. During the maintenance phase, the safety profile was similar across the treatment regimens, with the exception of increased infusion reactions observed in the 3 mg/kg as-needed treatment group. Neutralizing antibodies to infliximab were detected in 49 patients (35.8%) and 59 patients (41.5%) in the 5 mg/kg continuous and as-needed groups, respectively, and in 69 patients (51.5%) and 60 patients (46.2%) in the 3 mg/kg continuous and as-needed groups, respectively[5].

In another study, Reich et al.[6] evaluated the efficacy and safety of continuous versus intermittent infliximab maintenance therapy for psoriasis. However, more serious infusion-related reactions occurred with intermittent therapy (8 of 219 patients, 4%) than with continuous therapy (1 of 222 patients, $<$1%), prompting the sponsor to terminate the study. Greater rates of PASI75 responses were observed with continuous therapy (81 of 101 patients, 80%) than with intermittent therapy (39 of 83 patients, 47%)[6].

Risk of antibody formation with intermittent infliximab therapy is a particular concern[7,8]. A study focused on inflammatory bowel disease revealed episodic infliximab schedules may have led to the formation of anti-drug antibodies and in turn, may be the culprit to increased infusion reactions[8].

When to discontinue tumor necrosis factor antagonists and how to restart treatment

Although the current paradigm in psoriasis management favors continuous use of TNF antagonists, certain situations, such as increasing cost burden, poor adherence, elective surgery, and pregnancy, may warrant treatment interruption[1]. Additionally, we believe that clinical remission should also be considered a factor that may merit consideration of TNF inhibitor discontinuation.

Potential populations for biologic discontinuation have been previously examined. A consensus report[2] by a panel of psoriasis experts, comprised of 147 dermatologists from 33 countries, suggested the following patient subgroups to be considered candidates for biologic therapy discontinuation: patients 1) who prefer to stop treatment, 2) with a history of disease-free intervals or previously stable plaque-type psoriasis, 3) with no relevant comorbidities, 4) without psoriatic arthritis, 5) whose quality of life is not considerably affected by the disease, and 6) who did experience worsening disease after previous dose reductions and treatment withdrawals.

Although there are no curative therapies for psoriasis, many patients still perceive clinical remission as a realistic primary goal of psoriasis treatment. A formal definition of "clinical remission" in psoriasis has not been clearly proposed, and thus, there remains no consensus about its definition. Several standards of clinical remission have been documented. A majority of studies quantify disease remission as achieving PASI75 or a PGA of "clear" or "almost clear"[7], while there have been studies that use PASI50 as the standard for treatment interruption[11]. De-

spite these previous standards, with the increasing efficacy of new biologic treatments, PASI90 may become the new measure of optimal response.

Similar to the previous discussion on the need to define "clinical remission", the criteria for defining the duration of a sustained response have yet to be been elucidated. Some studies have considered treatment discontinuation when the treatment efficacy sustained for 16 or 20 week[12]. Other, more cautious researchers agree that stopping biologic therapy should be considered only after a minimum of one year of maintained remission[2].

Further studies to establish re-dosing treatment plans after TNF antagonist withdrawal are also warranted. In cases where therapy has been withdrawn and restarted, an induction doses should be used considered for the reintroduction of the biologic agent, with the possible exception of infliximab (due to the associated increased risk of infusion reactions)[2].

DISCONTINUATION OF TUMOR NECROSIS FACTOR ANTAGONISTS IN OTHER INFLAMMATORY DISEASES

Rheumatoid arthritis

Induction of TNF antagonists has led to remission of RA, and greater remission rates were achieved when TNF antagonists were used in combination with methotrexate. Despite these promising results, concerns about potential adverse effects have risen with the long-term use of TNF antagonists.

Only a few clinical trials have addressed the question of whether TNF antagonists can be withdrawn in patients with RA[3].

A 2016 review found discordant results among RA studies concerning the discontinuation of TNF antagonists, with the reported success rates ranging from 13% to 48% at 1 year after discontinuation[19]. The study found that approximately half of the patients with early RA could discontinue TNF-targeted biologic therapy without clinical flare and functional impairment after attaining low disease activity with a TNF antagonist and methotrexate. For established RA, however, fewer patients sustained low disease activity after the discontinuation of TNF antagonists[19].

In a 2015 registry study examining RA patients, discontinuation of the first course of TNF antagonist was associated with persistent clinical benefit. Half of the patients examined were able to maintain response through 20 months[3]. Discontinuation of medication was decided in patients who attained low disease activity or even lower levels of disease activity, defined as a Clinical Disease Activity Index (CDAI) score of ≤ 10[3].

However, the European League against Rheumatism (EULAR) 2016 recommendations do not appear to support idea of stopping biologic therapy even after remission of RA is achieved. Rather, EULAR suggests reducing dose or extension of interval, citing that discontinuation may lead to a recurrence of disease in most patients[20]. Nevertheless, greater than 80% of patients were able retain their initial response with retreatment[20]. Another review article in 2017 also favored tapering over withdrawal of biologic therapy in established RA[21]. This review suggested that the complete withdrawal of biologic therapy in patients with established RA does not result in sustained remission. Consistent with EULAR, the authors recommended the strategy of reducing the dose or frequency for established cases[21].

Historically, there have been disagreements about the definition of remission, the efficacy of tapering or withdrawal of drugs, and the strategy for monitoring relapse in RA[21]. To help achieve some clarity, American College of Rheumatology (ACR)-EULAR proposed two new remission criteria in 2011 on the basis of RA trial data: 1) Boolean-based definition, in which at any time point, the patient must satisfy all of the following[22]: tender joint count ≤ 1, swollen joint count ≤ 1, C-reactive protein ≤ 1 mg/dl, PGA score ≤ 1 (on a 0~10 scale); and 2) index-based definition, in which at any time point, the patient must have a Simplified Disease Activity Index (SDAI) score of ≤ 3.3.

From the recent guideline, tapering of disease-modifying anti-rheumatic drugs (DMARDs) or biologics should be considered if patients fulfill the standardized clinical criteria for remission (i.e., Disease Activity Score [DAS] 28 < 2.6, DAS44 < 1.6, SDAI < 3.3, CDAI < 2.8, ACR-EULAR remission), remain in remission for at least 6 months as assessed with appropriate disease activity instruments at 3 sequential visits, have used a stable type and dose of DMARD during the previous 6 months, and do not require glucocorticoids to maintain the remission[23,24].

Certain predictors (early RA, depth of improvement, and duration of remission) have been identified to predict a successful outcome after tapering or discontinuation of RA treatment[20,25]. Seropositivity, functional status, and disease activity at the time of TNF antagonist discontinuation were also considered key factors in maintaining the treatment benefits[3,19]. A history of stable dosing of biologics, absence of a requirement for corticosteroids for a defined period, DAS28 score, absence of synovitis, absence of radiographic progression, and low or zero swollen or tender joint count were additionally identified as factors for the dose-down strategy in RA[21].

Psoriatic arthritis

Similarly to RA, many physicians believe that discontinuation of biologics can be fully considered after the remission of psoriatic arthritis. However, compared with RA, there has been less evidence to support treatment decisions in psoriatic arthritis. Furthermore, there lacks validated remission criteria for psoriatic arthritis on which to standardize results from clinical studies and registry data. This has led to the use of different sets of criteria for remission assessment and different methods for selecting patients[26].

In a previous study, remission of psoriatic arthritis was defined based on the ACR RA remission criteria, in which at least a four-month period of maintenance is required to conclude disease remission[27]. Recently, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis developed and validated the criteria for minimal disease activity in psoriatic arthritis[28]. They included assessments of enthesis and skin, which are specific clinical domains for psoriatic arthritis. Newer measures for psoriatic arthritis, including the Psoriatic Arthritis Disease Activity Score, Composite Psoriatic Arthritis Disease Activity Index, and Arithmetic Mean of Desirability Functions for disease activity assessment have been introduced[29].

Furthermore, unlike for RA, there have been limited data about the interruption or dose reduction of TNF antagonists for psoriatic arthritis[21].

In 2003, Kane et al.[30] reported a cohort study of 129 patients with early psoriatic arthritis (mean disease duration, 9 months) who were taking traditional DMARDs. These patients showed a remission rate of 26% at one year and 21% at two years. In that study, 12% and 11% of patients maintained the state of drug-free remission at one and two years, respectively.

In 2008, Cantini et al.[27] reported a 24.1% remission rate in 236 patients with psoriatic arthritis. Remission was considerably more frequent in patients treated with TNF antagonists than in those treated with methotrexate alone (79.5% vs. 20.4%)[27]. No difference was noted between two groups in terms of the remission duration. Upon discontinuation of treatment, remission lasted for an average of 12 months.

In 2010, Saber et al.[31] reported that 58% of 152 patients treated with TNF antagonists achieved remission at 12 months. They found that a higher functional status at baseline was the best predictor for remission in patients with psoriatic arthritis.

In contrast, high rates of recurrence (76.9%) and shorter intervals before recurrence (74.50±51.72 days) were noted after interrupting methotrexate monotherapy or TNF antagonist therapy in an open-label study in 2015[32]. However, all recurred cases again attained remission after the re-initiation of treatment.

Recently, a pilot study was designed to test the feasibility of drug withdrawal in patients with psoriatic arthritis in the minimal disease activity state[33]. In this study, the withdrawal group underwent a stepwise phased withdrawal of medication, in which the last treatment added was the first withdrawn. However, most patients regained low disease activity after restarting the previous medication. Unfortunately, difficulty in patient recruitment and the relatively high relapse rate for both methotrexate and biologics hindered the performance of a subsequent large randomized controlled study[33].

In 2012, Cantini et al.[34] reported that reducing the adalimumab dose resulted in maintained clinical remission in 76 patients with psoriatic arthritis and in 55 patients with RA. Higher remission rates were achieved in patients with psoriatic arthritis than in those with RA, with both the standard dose and the reduced dose.

An abstract from ACR registry reported that the CDAI and PGA assessment may be helpful before deciding to taper TNF antagonist in patients with psoriatic arthritis[35].

Limitations

This study has some limitations. First, this review did not include all randomized controlled trials available within the literature. Second, there was heterogeneity in the designs of the reviewed studies. The definitions for disease remission and relapse amongst the studies were not standardized. Duration of disease, initial and concomitant treatments, and strategies for tapering the medication doses and intervals also varied. Lastly, as in RA and psoriatic arthritis, reduction in drug dose and/or the dosing interval can be a more efficient strategy in comparison to discontinuing therapy in a psoriasis patient successfully managed with TNF antagonists. However, the current review did not focus on this topic because there was little relevant data. In addition, anti-interleukin (IL) 12/23, anti-IL-17, and anti-IL-23 drugs were not included in this review, because of the paucity of information on recent developments. Nevertheless, we believe that continuous treatment should be considered the most effective option of therapy until further definitive results are published supporting intermittent therapy with these medications.

CONCLUSIONS

Herein, we address the question of whether it is possible to discontinue TNF antagonists after clinical remission of

psoriasis and retreat flares on an "as-needed" basis. We would like to emphasize that this review does not aim to exhibit the need for TNF antagonist discontinuation. Rather, our aim is to highlight the need for further studies to examine the possibility of TNF antagonists discontinuation while still maintaining remission in psoriasis.

In summary, although more patients on continuous TNF antagonist therapy attain PASI75 or PASI90 than those with intermittent use, the discontinuation of TNF antagonist therapy may well be considered when clinical remission is maintained for a certain period of time in patients with psoriasis. For some, this may minimize the economic burden and drug-induced adverse effects. Multiple studies examining both etanercept and adalimumab have indicated that patients, for whom treatment was discontinued and experienced subsequent disease exacerbation, were able to achieve comparable efficacy following retreatment, with few adverse effects. However, infliximab was found to be more effective and safer when used continuously for psoriasis.

In the event of associated risks with TNF antagonist discontinuation, clinicians can consider the options of increasing dosing intervals or decreasing medication dosage.

Patients should be evaluated on a case-by-case basis before treatment discontinuation, and careful monitoring is important after discontinuation.

Several challenges remain to achieve a more personalized approach to the future of psoriasis treatment. Further studies are warranted to define "remission" in moderate to severe psoriasis and to identify the specific characteristics of patients in whom treatment withdrawal can be successful.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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