
Continuous *versus* intermittent therapy for moderate-to-severe psoriasis

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ABSTRACT

Psoriasis is a chronic immune-mediated inflammatory disease of unknown etiology. Unlike other chronic inflammatory diseases receiving continuous treatment, psoriasis has traditionally been treated intermittently secondary to concern for cumulative toxicity of conventional systemic therapies. However, the development of targeted anti-inflammatory biologic agents allowed for continuous therapy for most patients. Herein, we review the literature for intermittent versus continuous use of widely available therapies for moderate-to-severe psoriasis: phototherapy, topical corticosteroids, conventional systemic therapies and biologic agents. These data support continuous treatment in biologic therapy, such as etanercept, adalimumab, infliximab, and ustekinumab. Intermittent therapy with biologic agents leads to decreased efficacy and sometimes increased side effects. When conventional systemic therapy is used continuously, it is more efficacious; however the data support intermittent use of methotrexate and cyclosporine due to cumulative toxicities. Psoriasis severity may wax and wane, but it is a chronic disease requiring continuous treatment for optimal control of inflammatory activity and to minimize cutaneous involvement.

Background

Psoriasis is a chronic immune-mediated inflammatory disease of unknown etiology with no known cure. Unlike other chronic inflammatory diseases receiving continuous treatment, such as diabetes, heart disease, and rheumatoid arthritis, psoriasis treatments often have been used intermittently secondary to issues including toxicity, inconvenience, cost, or other complicating medical conditions.

Intermittent phototherapeutics were long the mainstay of treatment for moderate-to-severe psoriasis, starting with

the Goeckerman Regimen in 1929 in which crude coal tar and sunlight were periodically applied (1, 2), and continuing with Ultraviolet-B (UVB) phototherapy and Psoralens plus Ultraviolet-A (PUVA) (3). Beyond its inconvenience, the carcinogenicity associated with PUVA limited its long-term use. Cost is also a factor potentially limiting the use of phototherapy. Methotrexate (MTX) and cyclosporine (CsA) (4) were among the first systemic therapies for psoriasis, but concern for their cumulative toxicity precluded continuous treatment by dermatologists (5, 6). In the early 1990s, the concept of drug holidays and life-long rotational therapy arose from an effort to minimize these risks and prolong the safe and permanent use of available treatment options (7).

As researchers identified pathogenic immune pathways and inflammatory mediators in psoriasis, targeted immune therapy emerged. With the development of TNF-alpha inhibitors, biologic agents entered the field as promising new treatment options for this disease (8). Compared to older and more traditional therapies, cytokine inhibitors were felt to lack the cumulative toxicity (9-12) and also work more effectively (13) than older oral agents. Despite a long history of intermittent and rotational therapies, many dermatologists now find continuous use of these new medications to be most effective (14, 15). Our aim is to evaluate continuous as compared to intermittent treatment of psoriasis.

Current FDA-approved therapies for psoriasis

Phototherapy

Current effective phototherapies include UVB, PUVA and the 308nm Excimer Laser. In our experience, remissions are longer than of those occurring after treatment with MTX, CsA, or topical treatments (16). One study reported that four weeks of five-times per week treatment with NB-UVB provided a

year or more of remission in 56% of patients (17). Phototherapy is the only non-topical treatment that may be used as needed for flares, however it is often ineffective when not dosed two to three times weekly (18). Guidelines suggest that any interruption of therapy for three weeks or more requires restarting phototherapy at its starting dose (19). The utility of this treatment modality is limited by lack of nearby access, inconvenient administration, and cost concerns in the form of frequent patient co-payments. In particular, although phototherapy costs the insurance company an average of \$5,713 per year, compared to an average of \$26,708 for biologic agents (20), the out-of-pocket cost to patients is up to \$3,040 annually for phototherapy compared to \$920 for biologic agents (21). Furthermore, PUVA therapy has independently been shown to be a strong risk factor for skin cancer (22), including melanoma (MM), for which there is a relative risk of 2.3 (95% CI=1.1-4.1) 15 years after first treatment in a high exposure cohort compared with controls (23); PUVA also leads to an odds ratio of 2.6–16.2 for the development of squamous cell carcinoma (SCC) (24–27). Secondary to the increased risk of skin cancer associated with PUVA, intermittent use is recommended because each patient should not exceed a set total exposure during their lifetime. In contrast, no significant increase in the risk of SCC was associated with long-term exposure to UVB or topical coal tar, nor was basal cell carcinoma associated with any form of phototherapy (28–30).

Topical corticosteroids

Topical corticosteroids are the most commonly prescribed treatment for psoriasis (18, 31). Their value is limited by poor long-term control (32), poor compliance (33), and cutaneous side effects (e.g. atrophy) that result from chronic use (34–36). One large meta-analysis illustrated sustained clearance rates of up to 78% for eight weeks of continuous therapy or 52 weeks of intermittent therapy with very potent steroids (37). However, another study showed that maximal skin clearance decreased to 50% in three months and to 29% in one

year of continuous use (38). Moreover, compliance is frequently an issue, with several studies showing non-adherence rates around 40% (35, 39, 40), and one study demonstrating that one-third of prescriptions for corticosteroids and 14.3% of systemic therapies are never redeemed (41). Seventy-nine percent of surveyed dermatologists viewed systemic and phototherapy to be far superior to topical steroids for the management of psoriasis (38).

Conventional systemic therapies

– Methotrexate (MTX)

MTX, a structural analogue of folic acid, is typically prescribed as a weekly 5–25 mg dose, but there have been several small studies of less frequent, intermittent dosing (42–44). A large study of 197 patients on intermittent MTX therapy demonstrated 90% clearance of psoriasis in over 85% of patients, with remission periods of up to 32.4 weeks (45). MTX has shown PASI-75 achievement rates of 35%–100% (10, 46–49). However, MTX is generally found to be less effective than the biologic agents for control of psoriasis (10) and is associated with cumulative hepatotoxicity. Long-term use of MTX may result in significant hepatotoxicity, including fibrosis and regenerative nodes, when taken in cumulative doses of 3–4g (50). However, weekly low dose (5–25mg) MTX is relatively safe for long-term use, as described in rheumatology literature (51). A retrospective analysis of 248 patients treated with 5–25 mg of MTX for rheumatoid arthritis reported a safety profile that is comparable to NSAIDs; this same group did report 111 patients who developed laboratory abnormalities, but only 27 of these cases were clinically significant, where nine patients had significant increases in AST and 11 had significant decreases in albumin (51). This retrospective analysis of patients with rheumatoid arthritis reported a 79% continuation rate (51), similar to studies in psoriasis that have documented at least 20% treatment discontinuation due to elevated liver enzymes and other side effects (52, 53), which may be mitigated by intermittent use (45, 54). Based on available data for MTX

toxicity, current guidelines from the American Academy of Dermatology (6) suggest that for patients without risk factors for hepatotoxicity (i.e. alcohol intake, obesity, hyperlipidaemia, diabetes, hepatitis), liver function should be evaluated monthly for the first six months and every one to three months thereafter, with stricter guidelines following prolonged use, including liver biopsy after 3–4 grams cumulative MTX dosing. Guidelines for rheumatology are less strict (55). If risk factors for hepatotoxicity are present, liver biopsy is indicated sooner.

– Cyclosporine (CsA)

CsA, a calcineurin inhibitor (56, 57), is a highly effective therapy in the treatment of psoriasis (58, 59). A large two-year study demonstrated satisfactory clinical improvement in 90% of patients after 12 weeks of therapy (60). Several studies comparing continuous versus intermittent treatment showed that continuous use maintained better control, but was also associated with higher toxicity (61, 62); in fact, more than 50% of patients experienced a significant increase in serum creatinine associated with irreversible changes on renal biopsy after two years of continuous use (63, 64). Several studies failed to find a difference in efficacy between intermittent and continuous treatment groups (62, 65), despite a 139% increase in required dose for those on continuous therapy (62).

Combination therapy has become a popular option to curtail cumulative toxicities and has shown good results with lower CsA doses (66–69). However, concerns for adverse effects remain; one study of 122 patients taking CsA for up to 76 months found that 14% discontinued treatment due to adverse events after 12 months and 41% after 48 months of treatment (70). CsA has also been associated with multiple malignancies (71–77), including an increased risk of developing SCC when used with PUVA (78). A 2004 consensus statement from a group of international dermatologists recommended intermittent CsA use for most patients, with continuous long-term use only recommended for those with recalcitrant

disease (58). Thus, current guidelines suggest that use of CsA be limited to two years or less (58).

– *Acitretin*

The oral retinoid acitretin is an available continuous treatment for psoriasis and has been found to decrease the risk of developing SCC in psoriasis patients treated with PUVA (79). However, as a single agent, acitretin does not clear psoriasis well. Acitretin is mild to moderately effective in psoriasis (PASI-75 rates of up to 69%) (80, 81), by thinning plaques and reducing affected body surface area (82). Acitretin is limited by its potent teratogenicity; pregnancy is contraindicated during and for three years following treatment (83). In our experience, intermittent therapy is difficult, as there is a long lead-time to see results and relapse typically occurs after approximately two months of treatment discontinuation.

Biologic agents (cytokine inhibitors)

Presently, three TNF antagonists are FDA-approved for use in psoriasis in the USA. All of these agents have been found to elicit greater and more sustained decrease in PASI score when used continuously. Ustekinumab, a human monoclonal antibody to IL-12 and IL-23, is the most recently approved biologic agent and has shown similar efficacy in treating psoriasis.

– *Etanercept*

Etanercept is a dimeric recombinant fusion protein, generated by linking two soluble extracellular domains of human

TNFR2 to the Fc portion of human IgG1. Etanercept was the first FDA-approved TNF inhibitor for psoriasis, and has a greater amount of literature supporting its use as continuous therapy. Clinical trials demonstrate greatest clearance and fewest adverse events with continuous therapy (summarised in Table II) (84-86) In clinical practice, relapses typically occur without toxicity-related adverse events or hospitalisations, approximately 12 weeks following discontinuation (86, 87). A post-hoc analysis of 226 patients receiving intermittent treatment found that while initial remission with etanercept may be achieved on average in 11 weeks, during re-treatment, remission requires on average, 15 weeks (88). Neutralising antibodies were not found to be significant in one study (86), and were not discussed in the other trials (84, 85). By contrast, two small studies found that intermittent treatment maintained efficacy even after reinduction (89, 90), but these studies were small and poorly controlled.

– *Adalimumab*

Adalimumab is a human monoclonal antibody to TNF-alpha, which results in up to 80% PASI-75 response in patients with psoriasis (91, 92). In the only study of intermittent therapy, a multicenter open-label study of 1468 patients by Papp *et al.* found that withdrawal from treatment was associated with disease relapse, and that only 69% of patients who relapsed were able to achieve clearance again after withdrawal and re-treatment (93). That study, found no difference in safety

between the continuous and intermittent groups, but that withdrawal was associated with a 2% risk of formation of anti-adalimumab antibodies (93). Other reports have shown a statistically significant correlation between anti-adalimumab antibodies and decreased response rate (94-96).

– *Infliximab*

Infliximab is a chimeric monoclonal antibody to TNF-alpha. Several clinical trials have found every eight week dosing to be more effective in achieving PASI 75 than as needed dosing over the course of one year of treatment (14, 15). In one study, the intermittent group experienced a higher incidence of serious infections and serious infusion reactions such that this arm of the study had to be terminated (15). Most patients with infusion reactions tested positive for antibodies to infliximab. In a study of infliximab for treatment of inflammatory bowel disease, patients on intermittent therapy were found to be more likely to develop auto-antibodies (97).

– *Ustekinumab*

Ustekinumab is a human monoclonal antibody-specific for the common p40 subunit of the cytokines IL-12 and IL-23. One study found that more patients achieved PASI 75 after 12 weeks with ustekinumab than with either placebo or etanercept (98). A large phase III, randomised, double blind, placebo-controlled study found that 50% of patients lost their previously attained PASI 75 after 16 weeks of withdrawal, whereas

Table I. Cyclosporine – Intermittent versus continuous comparison.

Authors	Continuous vs. Intermittent	Patients in arm	Duration of study	Percentage of patients achieving PASI-75	E-PAP ** score	Mean dose (mg/kg/day)	Patients experiencing severe adverse events
Chaidemenos <i>et al.</i> , 2007 ⁵²	Continuous	21	12 months	92%		3	2
	Intermittent	21	12 months	68%		1.8	2
Ohtsuki <i>et al.</i> , 2003 ⁵¹	Continuous	15	48 months+		6.39	3.24	2
	Intermittent	16	48 months+		9.01	2.78	0
Ozawa <i>et al.</i> , 1999	Continuous	50	36 months		5.19	3.20	1
	Intermittent	44	36 months		7.44	3.06	0

*Approximately 70% of Ohtsuki *et al.* patients could not be followed for 48 months; **E-PAP: A metric combining PASI score with number of days at that PASI level.

Table II. Biologics – Intermittent versus continuous comparison.

Authors	Treatment	Continuous vs. Intermittent	Dose	Patients in arm	Duration of study	Percentage of patients achieving PASI-75 at evaluation	Patients experiencing severe adverse events	Patients experiencing infusion-related reactions
Reich <i>et al.</i> , 2013 ^{10*} (RESTORE 2)	Infliximab	Continuous Intermittent	5 mg/kg q8wk 5 mg/kg q8wk prn if PASI<50	222 219	52 weeks	80% at 52 weeks 47% at 52 weeks	24 23	1 8**
Menter <i>et al.</i> , 2007 ⁹	Infliximab	Continuous	5 mg/kg q8wk	150	50 weeks	54.4% at 50 weeks	5	28
		Intermittent	5 mg/kg q8wk prn	149	50 weeks	38.1% at 50 weeks	3	30
		Continuous	3 mg/kg q8wk	148	50 weeks	43.8% at 50 weeks	6	29
		Intermittent	3 mg/kg q8wk prn	148	50 weeks	25.4% at 50 weeks	4	39
Moore <i>et al.</i> , 2007 ⁷⁴	Etanercept	Continuous	50mg qwk	1272	12 weeks	71% were PGA 0/1 at 12 weeks	37	
		Intermittent	50mg qwk starting either 4, 8, or never weeks	1274	12 weeks	59.5% were PGA 0/1 at 12 weeks	33	
Ortonne <i>et al.</i> , 2008 ^{75,78}	Etanercept	Continuous	25mg biw	357	54 weeks	1.98 Mean PGA over 54 weeks	23	
		Intermittent	25mg biw if PGA>2	363	54 weeks	2.51 Mean PGA over 54 weeks	31	
Leonardi <i>et al.</i> , 2008 ¹¹¹	Ustekinumab	Continuous	45 mg q3mo	77	36 weeks	–	1	
		Continuous	90 mg q3mo	85	36 weeks	–		
		Intermittent	45 mg q3mo prn	73	36 weeks	–	7	
		Intermittent	90 mg q3mo prn	87	36 weeks	–		

*Patients were retreated when they experienced loss of PASI-50. Study terminated by sponsor due to adverse events in intermittent arm.

**Primarily infusion-related reactions.

Table III. Biologics – Etanercept: time to relapse after withdrawal at various doses.

Authors	Treatment	Dose	Patients in arm	Duration of study	Patients who relapsed	Median days until relapse	Patients experiencing severe adverse events
Gordon <i>et al.</i> , 2006 ^{76***}	Etanercept	50 mg biw if PASI<50	122	36 weeks	103	122	1
		25 mg biw if PASI<50	202	36 weeks	171	107	3
		25 mg qwk if PASI<50	85	36 weeks	68	85	1

***Median time to relapse was 12 weeks.

Table IV. Biologics – Time to relapse after adalimumab withdrawal.

Authors	Treatment	Patients in arm	Duration of study	Patients who relapsed before 40 weeks of withdrawal	Median days until relapse	Percentage achieving clearance after 16 weeks of retreatment		Patients experiencing severe adverse events
						Experienced relapse before 40 weeks of withdrawal	No relapse before 40 weeks of withdrawal	
Papp <i>et al.</i> , 2011 ⁸³	Adalimumab	285	56 weeks	178	141	69%	89%	9

>80% of patients maintained PASI 75 for three years with continuous treatment. Anti-drug antibodies were found in 5.2% of patients after three continuous years, but there was no evidence of decreased clinical response as a result. Importantly, the authors found no signs

of cumulative end organ toxicity after three years of treatment (99). Although there is less available information as this is the most recent of the biologic agents to be approved, continuous treatment has been found to be the most effective option.

Discussion

The debate as to whether psoriasis should be treated continuously or intermittently has been confounded by a history of staggered therapies. Initial therapies for psoriasis were administered on a strictly “as-needed” basis. MTX and

CsA both demonstrate efficacy (10, 46-49, 58, 59) but there was also concern for hepatotoxicity and nephrotoxicity, respectively, when these agents were used continuously for extended periods of time. These toxicities are mitigated or delayed greatly with intermittent use, and thus, intermittent MTX and CsA use has been recommended.

For biologic agents, multiple studies with etanercept indicated a significantly higher proportion of patients attained PASI-75 with continuous than with intermittent, "as needed" therapy (84-86). For adalimumab, only 69% of patients who discontinued therapy were able to re-attain clearance following re-treatment (93). Infliximab and ustekinumab were both found to be more effective when used continuously and also with fewer side effects. Taken together, current data support the use of continuous biologic therapy due to improved efficacy and safety.

Although the current paradigm in psoriasis management favors the use of biologic agents continuously, patients and/or clinicians may need to interrupt or terminate treatment due to cost burden, poor adherence, elective surgery, and pregnancy. Biologic therapies are generally more expensive, with one comparison estimating the annual per-patient MTX cost to the healthcare system at \$1330 as compared to an average biologic cost of \$26,708, but up to \$48,731 for more frequent dosing with high-dose etanercept (20). A study of 1095 patients in the United States, with insurance plans, suggested that less than 5% of patients stop biologic agents because of cost and up to 34% stop biologic agents because of poor efficacy or loss of efficacy (100). However, another study suggested that a significant portion of patients at lower income levels were forced to cut back on personal expenses in order to continue taking a biologic agent, due to an annualised out-of-pocket cost of \$557.12 (101). Despite their increased cost, biologic agents may contribute to decreased overall healthcare utilisation and increased patient productivity (102), by optimising disease control and minimising psoriasis-associated health disabilities.

One study indicated that good patient adherence to biologic therapy decreased overall costs (103), suggesting that continuous therapy with its inherent high compliance could lead to cost benefits compared to intermittent therapy. A systemic literature review of five studies suggested patient compliance was highest for biologic therapies, followed by oral agents, phototherapy, and topical treatments (104). Of note, patient satisfaction with treatment has been strongly associated with compliance (104-106).

The effect of biologic agents on wound healing and post-operative infection has provoked clinical concern for their use in surgical patients. Animal wound-healing models have demonstrated a concentration-dependent role of TNF on wound healing and strength. While lower concentrations of TNF have been associated with improved angiogenesis, collagen synthesis and healing (107-109), high concentrations have been associated with decreased wound strength and even the chronicity of venous leg ulcers (110-114). Most available data on the perioperative use of biologic agents in humans is derived from small retrospective studies that evaluate the risk associated with TNF inhibition in inflammatory bowel disease and rheumatoid arthritis patients. Although, the majority of these studies have not found an increased risk of wound dehiscence or infection, the studies are statistically underpowered (115).

Pregnancy and lactation may be other reasons for treatment discontinuation in psoriasis. All TNF inhibitors approved for psoriasis in the USA contain an IgG Fc portion. Therefore, they can very effectively cross the placenta during the second and third trimesters and potentially affect the developing foetus. Since the half-life of immunoglobulins is up to several months in children, a potential increased risk for infection exists, which may necessitate delaying their scheduled live attenuated vaccinations (116). Thus, one reviewer suggests biologic agents should be discontinued before 30 weeks gestation (117). However, despite the theoretical risk of infection, studies from 2010 to 2012 have shown that infliximab and adalimumab

use during pregnancy does not increase the overall risk of congenital malformations (118). Biologic therapies are class B, and may therefore be used during pregnancy, but use is ultimately at the discretion of the obstetrician. As an alternative to biologic agents, evidence supports the use of NBUVB or CsA for psoriasis treatment during pregnancy (117).

Conclusion

Herein we address the question as to whether psoriasis treatments should be given continuously or "as needed" for flares. Continuous therapy is more efficacious than intermittent use of available psoriasis therapies, although rotational therapy remains appropriate for treatments with cumulative toxicities. The high cost of newer drugs such as biologic agents makes continuous use a large economic burden, but the improved quality of life and productivity resulting from disease control may decrease overall healthcare costs. Adherence and satisfaction appear to be greater for biologic agents when compared to other therapies, with only a minority of patients discontinuing therapy due to cost burden. There is no consensus on the use of biologics perioperatively and during pregnancy. This new paradigm of biologic agents establishes that psoriasis is a chronic inflammatory disease and therefore requires lifelong and chronic treatment in order to maintain remission.

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