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Biologic Discontinuations Studies: A Systematic Review of Methods

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Abstract

Objectives—We conducted a systematic review to assess the design and “failure definition” in studies of biologic discontinuation in rheumatoid arthritis (RA).

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Methods—We found 403 studies on PubMed, and included 9 published papers and 5 abstracts from scientific meetings. We used a structured extraction form to collect information regarding study design and outcome (failure) definition.

Results—Three types of studies were found: randomized controlled trials, long-term extension studies of clinical trials, and prospective discontinuation studies. The largest study had 196 subjects in the discontinuation arm. Most studies allowed concomitant use of non-biologic drugs at biologic discontinuation. Heterogeneity was also found in the failure definition. Although all studies used measures of disease activity, the threshold for failure and the time point of assessment differed among studies. Few studies incorporated changing use of non-biologic drugs or glucocorticoids into the failure definition.

Conclusions—Although many studies have examined the outcome of biologic discontinuation, they have all been relatively small. Typical practice studies from registries may add important information, but will likely need to rely on a broader failure definition.

Keywords

biologic DMARDs; remission; discontinuation; rheumatoid arthritis

INTRODUCTION

Aggressive treatment strategies utilizing biologic disease modifying anti-rheumatic drugs (DMARDs) revolutionized the treatment of rheumatoid arthritis (RA). Remission or low disease activity is now a realistic goal for most patients. After achieving this disease state, it remains unclear whether biologic DMARDs should be continued indefinitely or discontinued.

Many studies have evaluated biologic discontinuation. However, comparing results from these studies is difficult due to heterogeneous designs and non-uniform definition for failing biologic discontinuation (“failure definition”). Also most studies have focused on RA patients enrolled in biologic trials or standardized protocols, which may not reflect typical practice. To address these issues, rather than focusing on the study results, we evaluated the *study designs* and *outcome (failure) definitions* used in prior studies of biologic discontinuation.

METHODS

Literature Search

We conducted a systematic review of literature. PubMed was searched for the following terms: (rheumatoid OR “Arthritis, Rheumatoid”[Mesh]) AND (TNF OR “tumor necrosis factor” OR abatacept OR adalimumab OR anakinra OR certolizumab OR etanercept OR golimumab OR infliximab OR rituximab OR tocilizumab) AND (withdrawal OR discontinuation OR stop). The search period was limited from 1998 (year when the first biologic DMARD was approved) to April 6, 2013. To include recent studies, abstracts presented at the 2010–2012 meetings of American College of Rheumatology and European

League Against Rheumatism were also searched. Only materials available in English were considered.

Titles of all identified studies were reviewed by one author (K.Y.). The exclusion criteria included (Figure 1): studies that did not use biologics, animal or in vitro studies, non-RA studies, reviews without primary data, studies not focusing on discontinuation of biologic DMARDs, studies that examined biologic discontinuation for side effects, studies that did not report outcomes after biologic discontinuation for good disease control, studies with less than 5 subjects, pediatric studies, and meeting abstracts without enough publicly available details.

Data Extraction

Data were extracted for study characteristics. We focused specifically on two aspects of the methods: *study design* and *outcome (failure) definition*. Each study's *study design* was assessed for sample size of discontinuation arms, study type, presence of controls who continued biologic DMARDs, focus on early arthritis, requirements before biologic discontinuation; concomitant non-biologic DMARDs and glucocorticoid use. We also described the *outcome (failure) definition* used to assess failure after biologic discontinuation. These included disease activity thresholds, when and how often the outcome was assessed, and composite failure definition, such as biologic reuse, non-biologic treatment modification, and radiographic outcomes. The outcome of the proportion of patients free of failure at 12 months (6 or 7 months result if 12 months result is not available) was also described.

RESULTS

Literature search results

We initially identified 403 abstracts in PubMed (last searched on April 6, 2013). After applying exclusion criteria (see Figure), 9 studies were considered relevant. Additionally, after exclusion of 3 published studies, 5 abstracts had sufficient details to be included, resulting in 14 total studies [1–14].

Study Design

The studies were from Europe (n = 8) [1, 2, 5, 6, 8, 10, 12, 14], from Japan (n = 4) [3, 7, 11, 13], and the US and Europe (n = 1) [9]. The sample sizes in the biologic discontinuation arms varied from 9 to 196. Three types of studies were identified (Table 1): randomized controlled trials ("RCT" in Table 1) [1, 2, 5, 9], in which discontinuation was randomized; long-term extension of trials ("LTE" in Table 1) [3, 6, 10, 14]; and single arm prospective studies of discontinuation ("DC study" in Table 1) [7, 8, 11–13], in which patients were prospectively recruited for biologic discontinuation.

Five studies had control arms, in which patients in good disease control were kept on biologic treatment [1–3, 5, 9]. Four studies randomized discontinuation [1, 2, 5, 9], and three used placebo in place of discontinued biologic treatment and provided at least double

blinding [1, 5, 9]. Four studies focused on early RA patients with less than 1 year of disease [6, 9, 10, 14], whereas the other studies were conducted on more established RA patients.

Biologic DMARDs were discontinued after pre-specified duration of use in two studies [6, 14]. All other studies used disease activity lower than a specific cut off as enrollment criteria. However, the disease activity measures and thresholds varied by study. In one of the studies, biologic discontinuation was assessed as part of biologic dose reduction protocol [8], i.e., biologic DMARDs were tapered after 6 months of good disease control until discontinuation or failure occurred, and failure of both tapering and discontinuation were reported. Another study had a similar tapering protocol, however, only discontinuation was reported [10]. Two studies addressed maintenance treatment with half-dose biologic DMARDs as well as discontinuation [1, 5].

Use of concomitant non-biologic DMARDs and glucocorticoids at the time of biologic discontinuation varied. Some studies required patients to be off glucocorticoids [7, 9, 10, 13, 14], whereas other studies allowed small doses of glucocorticoids (prednisolone-equivalent, < 10 mg/day [1, 2, 6] or < 5mg/day [11, 12]). In general, few details were provided about concomitant treatment in many of the studies.

Outcome (Failure) Definition

After discontinuation of biologic DMARDs, all RA studies used disease activity thresholds as failure criteria (Table 2). The cutoff for failure was either low disease activity or remission, but three studies used a relative definition either by itself [8] or in combination [2, 5]. The follow-up duration and time of assessment also varied. Most non-interventional studies (LTE study type) defined failure as increase of disease activity above the threshold at any time (time to failure analysis), whereas most interventional studies (RCT and DC studies) assessed disease activity at a pre-specified time [2, 3, 5–7, 9, 14], e.g., 6 months after discontinuation [6].

Biologic DMARD reuse was regarded as failure in all studies except for 4 studies in which reuse was not allowed [1, 6, 9, 14]. In most studies, reuse was according to protocol, i.e., reuse was allowed only after patients were labeled as failed by the main definition [2, 4, 5, 7, 8, 10, 12]. Treatment changes in non-biologic treatments at the discretion of the treating physician – increased doses or new introduction of non-biologic DMARDs and glucocorticoids– were used as failure definition in some studies [5, 7, 11], but only two studies reported changes in these treatments in detail [3, 8]. Two studies used radiographic progression as part of the failure definition [9, 11] although the cutoffs chosen may be arguable considering they were lower than the general smallest detectable differences between readers [15].

The actual outcomes of the studies varied widely (Table 2).

DISCUSSION

We reviewed studies on biologic discontinuation to examine their designs. We found heterogeneity across studies, particularly in study design and outcome (failure) definition.

Study enrollment was usually based on disease activity lower than a given threshold, but this threshold differed across studies. The failure definition was consistent in using disease activity measures primarily. However, concomitant non-biologic treatment at discontinuation and treatment changes after discontinuation were not sufficiently reported in most of the studies, and few clearly defined changes in non-biologic treatments as failure. The “success rates” during the first year varied from 0% to 80%, supporting the substantial heterogeneity noted as regards study methods. In fact, this is precisely why we focused this systematic review on study methods and not on results. While we believe the results of these studies to be very important, the methods need critical appraisal before considering how to interpret results appropriately.

To collect comparable information, use of standardized enrollment and failure definition is essential. Only very recently, RCTs that include biologic continuation control arms have been presented. These are very useful to study “comparative effectiveness” of biologic discontinuation in comparison to biologic continuation. However, such trials apply strict inclusion criteria, creating study cohorts that may not be generalizable. Thus, observational data from registries of typical practice could potentially contribute more clinically relevant information.

There are particular obstacles to registry studies. Increase of disease activity may occur between study visits and may not be present at the subsequent study visit, making it difficult to define “failure” only by disease activity at study visits. This “interval failure” issue may be partly addressed by including treatment modification as part of composite failure definition (disease activity increase OR treatment modification as failure). This approach is in agreement with preliminary RA flare consensus proposed by the OMERACT, which described flare as increase in disease activity that results in treatment modification [16]. However, as there is no consensus on what treatment changes should be considered clinically significant, there is inherent subjectivity in this definition.

In conclusion, the currently available studies show heterogeneity in designs, and suggest need for standardized definitions of biologic discontinuation in good disease control and failure of biologic discontinuation. Standardized failure definition incorporating changes in treatments in addition to the main criteria by disease activity may allow information from currently available clinical practice registries to be utilized, thereby providing information more relevant to typical clinical practice.

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Figure 1.

Selection of Studies.

Abbreviations. RA: rheumatoid arthritis.

Literature published after approval of the first biologic disease-modifying anti-rheumatic drug and meeting abstracts in the past three years were searched. Steps are explained in the method section of the text.

Table 1

Comparison of *study designs* of biologic discontinuation studies.

Study	Country	Biologic	Design		Discontinuation criteria			Concomitant drugs at discontinuation		
			Sample size *	Study type [†]	Control group [‡]	Early RA [§]	Duration of bio use		Activity measure	Required duration in good control
PRESERVE [1]	Europe	ETN	196	RCT	Yes	No	8 mo	DAS28-ESR < 3.2	Single time point [¶]	100%/25%
ADMIRE [2]	Sweden	ADA	15	RCT	Yes	No	Median 43.3 mo	DAS28-ESR < 2.6	3 mo	100%/...
BRIGHT [3]	Japan	ADA	22	LTE	Yes	No	Mean 45.8 mo	DAS28-CRP < 2.7	Single time point	13.6%/40.9%
CERTAIN [4]	Europe	CZP	18	LTE	No	No	6 mo	CDAI < 2.8	1 mo	100%/...
DOSERA [5]	Europe	ETN	23	RCT	Yes	No	Mean 35.3 mo	DAS28-ESR < 3.2	11 mo	100%/...
HIT HARD [6]	Germany	ADA	82	LTE	No	Yes	6 mo	None ^{**}	NA ^{**}	100.0%/...
HONOR [7]	Japan	ADA	51	DC study	No	No	Mean 16.6 mo	DAS28-ESR < 2.6	6 mo	100%/0%
van der Maas [8]	Netherlands	IFX	12	DC study	No	No	Mean 67.2 mo	DAS28-ESR < 3.2	6 mo	68.0%/4.0%
OPTIMA [9]	U.S./Europe	ADA	102	RCT	Yes	Yes	6.5 mo	DAS28-CRP < 3.2	1 mo	100%/0%
BeSt [10]	Netherlands	IFX	104	LTE	No	Yes	Median 11 mo	DAS < 2.4	6 mo	100%/0%
RRR [11]	Japan	IFX	114	DC study	No	No	Median 18.5 mo	DAS28-ESR < 3.2	6 mo	100%/28.1%
Brocq [12]	France	ADA/ETN/IFX	21	DC study	No	No	Mean 40.3 mo	DAS28-ESR < 2.6	6 mo	67.0%/14.3%
Nawata [13]	Japan	IFX	9	DC study	No	No	Median 17.5 mo	DAS28-ESR < 2.6	6mo	100.0%/0%
Quinn [14]	U.K.	IFX	10	LTE	No	Yes	12 mo	None ^{**}	NA ^{**}	100.0%/0%

ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; IFX: infliximab; RA: rheumatoid arthritis; DMARDs: disease modifying anti-rheumatic drugs; Steroids: glucocorticoids; NA: not applicable; ... missing.

*Sample size in the discontinuation arms.

[†]RCT: randomized controlled trials of discontinuation with continuation controls; **LTE**: long-term extension of trials; **DC study**: prospective single-arm studies of discontinuation, in which patients were recruited for biologic discontinuation.

[‡]Presence of biologic continuation control group.

[§]Focus on early rheumatoid arthritis mentioned by authors.

[¶]DAS28-ESR < 3.2 at week 32 and mean DAS28-ESR during weeks 12 to 32 < 3.2 were required.

^{**}Biologic DMARDs were discontinued at 24 weeks and 54 weeks in these studies, regardless of disease activity or duration in good control.

Table 2

Comparison of *outcome (failure) definitions* of biologic discontinuation studies.

Author	Main failure definition		Composite failure definition			Outcome
	Disease activity measure	Time of assessment* (interval)	Biologic reuse as failure	Non-biologic treatment changes as failure†	X-ray progression as failure‡	
PRESERVE [1]	DAS28-ESR > 3.2	at 12 mo	Not allowed	Not allowed	No	42.6% at 12 mo
ADMIRE [2]	DAS28-ESR > 2.6 or > 1.2	at 7 mo	Yes¶	...	No	33.3% at 7 mo
BRIGHT [3]	DAS28-CRP > 2.7	at 12 mo	Yes	No	No	18.2% at 12 mo
CERTAIN [4]	CDAI > 2.8	within 7 mo (...)	Yes¶	...	No	17.6% at 7 mo
DOSERA [5]	DAS28-ESR > 3.2 and > 0.6	at 12 mo	Yes¶	Yes	No	13.0% at 12 mo
HIT HARD [6]	DAS28-ESR > 2.6	at 6 mo	Not allowed	Not allowed	No	42.4% at 6 mo
HONOR [7]	DAS28-ESR > 2.6	within 12 mo (...)	Yes¶	Yes	No	38.3% at 12 mo
van der Maas [8]	DAS28-ESR > 0.6	within 7 mo [§] (q2mo + as needed)	Yes¶	No	No	0% at 7 mo
OPTIMA [9]	DAS28-CRP > 2.6	at 12 mo	Not allowed	...	mTSS > 0.5/yr	43.0% at 12 mo
BeSt [10]	DAS > 2.4	within 96 mo [§] (q3mo)	Yes¶	No	No	80.0% at 12 mo
RRR [11]	DAS28-ESR > 3.2	within 12 mo (q1-3mo)	Yes	Yes	mTSS > 0.5/yr	36.8% at 12 mo
Brocq [12]	DAS28-ESR > 3.2	within 12 mo (q1mo)	Yes¶	Not allowed	No	25.0% at 12 mo
Nawata [13]	DAS28-ESR > 2.6	within 29 mo [§] (...)	Yes	Not allowed	No	44.4% at 12 mo
Quinn [14]	DAS28-ESR deterioration	at 6 and 12 mo	Not allowed	...	No	70.0% at 12 mo

DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ¶/u: follow-up; mTSS: modified total Sharp score; : change in disease activity; ... missing.

*Assessment for failure “at” pre-specified time points or any time “within” the follow up duration (survival analysis). Assessment interval is indicated in a parenthesis for “within”-type studies.

†Treatment modification of non-biologic disease-modifying anti-rheumatic drugs and glucocorticoid at the discretion of the treating physician as part of composite failure definition.

‡X-ray progression as part of composite failure definition.

§Follow-up duration varied.

¶Biologic DMARD reuse was according to protocol, i.e., reuse was allowed only after being labeled as failure by disease activity criteria.

**Defined at 12 months (6 or 7 months if 12 months result is not available). As discussed throughout the article, these results are obtained by different outcome definitions.