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Limits of add-on trials: antirheumatic drugs

Laura Ottolenghi · Vittorio Bertele^{*} · Silvio Garattini

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Abstract

Purpose This paper assesses the design of clinical studies used in the process of regulatory approval, focusing on how add-on studies affect regulatory decisions.

Methods The sample case taken is that of the new agents for rheumatoid arthritis (RA) authorised by the European Medicine Agency (EMA). The European Public Assessment Reports (EPARs) accompanying the marketing authorisations were the source of information on the studies presented in the registration dossiers.

Results The recently approved anti-RA agents are all indicated in combination with methotrexate (MTX) for treating adults with active RA who have responded inadequately to disease-modifier drugs (DMARDs). The add-on design was frequently used in registration studies. For infliximab, etanercept, adalimumab and rituximab, add-on trials contributed, together with parallel-group trials, to gaining the approval as combination therapy. Anakinra and abatacept were authorised on the basis of add-on trial results only.

Conclusions Add-on trials do not allow assessment of the intrinsic efficacy and safety of new agents and their value as alternatives to available treatments. The indications granted for the new anti-RA agents do not specify whether newer drugs can replace standard treatments in nonresponders, can do better in the overall patient population or can be used as first-line treatment.

Keywords Add-on studies · Registration trials · Marketing authorisation · European Medicine Agency · Rheumatoid arthritis · Disease-modifying antirheumatic drugs · Infliximab · Etanercept · Adalimumab · Rituximab · Anakinra · Abatacept · Methotrexate

Abbreviations

A	new drug
B	active comparator
PLB	placebo
ABA	abatacept
ACR	American College of Rheumatology criteria
ADL	adalimumab
ANK	anakinra
AUC	Area under the curve
CHF	chronic heart failure
Cl	clearance
CTX	cyclophosphamide
CYP	cytochrome P450
DAS	disease activity score
DB	double-blind
DMARD	disease modifying antirheumatic drug
EMA	European Medicine Agency
EPAR	European Public Assessment Report
ETN	etanercept
IFX	infliximab
LFE	leflunomide
MA	marketing authorisation
MTX	methotrexate
NS	not significant
NSAID	nonsteroidal anti-inflammatory drug
PG	parallel group
RCT	randomised clinical trial
RTM	rituximab
RA	rheumatoid arthritis
SAE	serious adverse event
SSZ	sulphasalazine
TNF	tumour necrosis factor

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Introduction

The principle behind the need for combination therapy is to use drugs with different mechanisms of action together to

increase efficacy without increasing toxicity in multifactorial diseases such as diabetes, hypertension, etc. This is the case with rheumatoid arthritis (RA) also, in which patient responses to standard treatments tend to vary. The European Medicine Agency (EMA) guidelines of 2003 (CPMP/EWP/556/95 rev1/Final) recommend that approval of new antirheumatic drugs for RA should be based on proof of efficacy from adequately designed parallel group randomised trials against placebo, or comparative studies against an established active comparator. Combination therapy is also accepted, as this strategy “is gaining popularity”, provided that therapeutic claims, pharmacological rationale and investigation on drug interactions are presented. “Add-on placebo therapy may also be used when study design requires placebo and allows for combination with other effective treatment”.

Following on from our previous critical evaluation of regulatory criteria for marketing approval of antirheumatic drugs [1], this paper focuses on how add-on studies influence regulatory decisions, examining the design of clinical studies used in the process of EMA regulatory approval of new anti-RA agents.

Methods

Information on each anti-RA drug approved by the EMA from 1995 to 2007 was collected from the European Public Assessment Reports (EPARs), Scientific Summary (www.emea.europa.eu/index/indexh1.htm), and completed with the published papers on the trials that provided the basis for approval. These trials were reviewed with particular attention to study design, type of comparator used, combination therapy and inclusion criteria and are grouped according to the comparators used or their combinations.

Results

Seven anti-RA [one nonbiological, three tumour necrosis factor (TNF)- α blockers—infliximab (IFX), etanercept (ETN) and adalimumab (ADL)—the interleukin (IL)-1 blocker anakinra (ANK), the anti-CD20 antibody rituximab (RTM) and the selective co-stimulation modulator abatacept (ABA)] were granted a marketing authorisation (MA) by the EMA. Table 1 reports the main characteristics of the pivotal clinical studies submitted to EMA: leflunomide (LFE) [2], the only nonbiological disease modifying antirheumatic drug (DMARD) and the first to be approved (1999), was authorised on the basis of four phase III trials [3–6] including placebo and active controls [methotrexate (MTX) and sulphasalazine (SSZ)], although only superiority over placebo was demonstrated.

ETN [7] gained approval in 2000 as monotherapy or in combination with MTX in patients inadequately responding to a DMARD, with two phase III studies vs. placebo [8, 9] and one phase II/III add-on study [10]. Indication for treatment (in combination with MTX) of early RA patients not previously treated with MTX followed in 2004, with two phase III studies [11, 12] comparing ETN and MTX and with the combination of the new agent and MTX. An add-on study supported approval of the 50-mg strength (2005) [13].

The clinical trial programme for the initial authorisation (2000) of IFX [14] encompassed six clinical studies, the pivotal one being a phase III add-on study [15], which demonstrated the superiority of the combination in active RA patients inadequately responding to a DMARD (MTX). The extension of indication for early RA in patients not previously treated with MTX or other DMARDs (2001) was based on one clinical trial [16] comparing the combination of IFX and MTX with MTX plus placebo in MTX-naïve patients.

ADL [17] was approved in 2002 for treating patients inadequately responding to MTX on the basis of four studies, two that were placebo-controlled [18]; one primarily a safety study; and two add-on trials [19, 20]. In MTX-naïve patients, a phase III RCT supported the combination of ADL and MTX (2005) [21].

ANK [22] in combination with MTX received approval (2002) on the basis of two add-on randomised clinical trials (RCTs) [23, 24] and one dose-finding study lasting 24 weeks (not reported in Table 1).

RTM [25] in combination with MTX is indicated for severe active RA in patients inadequately responding or intolerant to DMARDs, including one or more TNF inhibitors (2006). The clinical programme included one phase III add-on trial and two supportive phase II studies: one comparative vs. MTX and one add-on.

ABA [26], the latest to be approved (2007), with an indication similar to RTM, presented a clinical development programme including three studies providing the main efficacy data and three with additional efficacy/safety information: a phase IIA pilot dose-finding monotherapy (not reported in Table 1), a phase IIB exploratory, and a phase III study. One further pivotal trial was submitted during evaluation of the MA application. As stated in the EPAR, it was designed “to validate the efficacy responses and to directly compare the safety profile of ABA-MTX and IFX-MTX combinations and placebo rather than to demonstrate noninferiority or superiority of ABA compared to infliximab”. In all studies, ABA was tested as add-on to background therapy with MTX, DMARDs or anti-TNF.

On the whole, comparison with placebo was the topic of four trials, mainly dose ranging, of ETN and ADL (Table 2). LFE (four studies) and ETN (one) were compared with but

Table 1 Registration trials in rheumatoid arthritis according to study design

Drug	Inclusion criteria	Concomitant medication	treatment	No. patients	trial design, duration (weeks)	Efficacy primary endpoint
A vs. PLB						
Etanercept [7]	DMARD failing patients (washout 1 month)	NSAIDs corticosteroids	ETN 2 doses tw vs. PLB	234	Phase III RCT, DB, PG 24 [8]	ETN 25 mg $p < 0.001$ vs. PLB
	DMARD failing patients (washout 4 weeks)	NSAIDs corticosteroids	ETN 4 dosing regimens vs. PLB	599	Phase III RCT, DB, PG 12 [9]	All dosing regimens significantly more effective than PLB
Adalimumab [17]	DMARD failing patients (mainly MTX), washout of all prior treatment	None	ADL 4 dosing regimens vs. PLB	544	Phase III RCT, DB, PG 26 [18]	ACR 20: ADL 40 mg eow/weekly $p \leq 0.001$
Safety study	DMARD failing or DMARD-naïve patients	Any DMARD except azathioprine, cyclosporine, anti-TNFs	ADL 40 mg eow vs. PLB	630	Phase III RCT, DB 24	No specific concern on concomitant use of DMARDs ACR 20 (secondary endpoint) response superior to PLB
A vs. B (vs. PLB)						
Leflunomide [2] extension study	DMARDs washout	NSAIDs, low-dose corticosteroids	LFE vs. SSZ	197	Phase III RCT, DB, PG 24 [3]	efficacy comparable with SSZ
	DMARDs washout-naïve patients about 2/3	NSAIDs, low-dose corticosteroids	LFE vs. SSZ vs. PLB	358	Phase III RCT, DB, PG 24 [4]	LFE significantly superior to PLB. NS vs. SSZ
Etanercept [7] early RA	DMARDs washout 10% patients, DMARDs washout	NSAIDs, low-dose corticosteroids	LFE vs. MTX	999	Phase III, equivalence RCT, DB, PG 52+52 [5]	LFE significantly less effective than MTX
	DMARDs washout-naïve DMARDs washout	NSAIDs corticosteroids folate supplementation	LFE vs. MTX vs. PLB	482	Phase III RCT, DB, PG 52 [6]	LFE significantly superior to PLB. NS vs. MTX
	DMARDs washout-naïve patients	NSAIDs corticosteroids folate supplementation	ETN 2-weekly dosing regimens + PLB vs. MTX + PLB	632	Phase III RCT, DB, PG 52 [11]	Radiographic progression results NS different between treatment groups
	DMARDs washout 4 weeks					
A vs. B vs. A + B						
Etanercept [7]	DMARDs other than MTX nonresponders	Folate supplementation	ETN 25 mg tw vs. MTX vs. ETN + MTX	682	Phase III RCT, DB, PG 52 [12]	24 weeks: ACR-N AUC ETN + MTX $p < 0.01$ vs. ETN and MTX
Adalimumab [17] early RA	DMARDs (67.5%) (washout for DMARDs)	Folate supplementation	ADL 40 mg eow + PLB vs. ADL + MTX vs. MTX + PLB	799	Phase III RCT, DB, PG 104 [21]	Week 52: ACR 50 response ADL + MTX $p < 0.001$ vs. ADL + PLB and MTX + PLB
Rituximab [25] supportive	DMARDs inclusive anti-TNF, nonresponders		RTM vs. MTX vs. RTM + CTX vs. RTM + MTX	161	Phase IIa RCT, DB, PG 24+80	ACR 50: RTM + CTX and RTM + MTX statistically superior significantly
A + B vs. B + PLB						
Infliximab [14] early RA	MTX-naïve patients	Folate supplementation?	IFX 2 doses + MTX vs. PLB + MTX	1004	Phase III RCT, DB, PG 54 [16]	ACR response: combination $p < 0.001$ vs. MTX
Add-on						
Infliximab [14] pivotal	MTX nonresponders (on stable MTX for 30 weeks)	Corticosteroids NSAIDs	MTX + PLB vs. MTX + IFX 4 doses	428	phase III RCT, DB, PG 54+48 [15]	ACR 20: each group $p < 0.0001$ vs. control
Etanercept [7]	DMARDs nonresponders MTX stable dose 4 weeks	folate supplementation NSAIDs folate supplementation	MTX + PLB vs. MTX + ETN 25 mg tw	89	Phase II/III RCT, DB, PG 24 [10]	ACR 20: ETN + MTX $p < 0.001$ vs. MTX
	MTX stable dose 28 weeks	50% on MTX corticosteroids NSAIDs	MTX + PLB vs. MTX + ETN 25 mg tw vs. MTX + ETN 50 mg	420	Phase III RCT, DB, PG 16 [13]	Safety and efficacy comparable

Table 1 (continued)

Drug	Inclusion criteria	Concomitant medication	treatment	No. patients	trial design, duration (weeks)	Efficacy primary endpoint
Adalimumab [17]	1 DMARD nonresponders on MTX for 6 months, stable 4 weeks	Corticosteroids NSAIDs folate supplementation	MTX + ADL 3 doses eow vs. MTX + PLB	271	Phase III RCT, DB, PG dose ranging 24 [19]	ADL + MTX $p < 0.001$ vs. PLB
pivotal	MTX nonresponders (on stable DMARDs washout)	Corticosteroids NSAIDs	MTX + ADL 2 doses eow/weekly vs. MTX + PLB	619	Phase III RCT, DB, PG 52 [20]	ADL + MTX $p < 0.01$ vs. PLB
Anakinra [22]	MTX for 6 months, on stable dose for 3 months	Corticosteroids NSAIDs stable 4 weeks	MTX + ANK 5 doses vs. MTX + PLB	419	RCT, DB, PG 12+12 [23]	ACR 20 week 12: ANK + MTX $p = 0.001$ vs. MTX + PLB
pivotal confirmatory	MTX for 24 weeks	Corticosteroids NSAIDs stable 4 weeks folate supplementation	MTX + ANK 100 mg vs. MTX + PLB	506	RCT, DB, PG 24 [24]	ACR 20: ANK + MTX $p < 0.001$ vs. MTX
Rituximab [25]	1 anti-TNF and < 5 DMARDs nonresponders	Infusional/oral corticosteroids folate supplementation	MTX + RTM vs. MTX + PLB	520	Phase III RCT, DB, 24+80	ACR 20: RTM $p < 0.0001$ vs. PLB
pivotal	1 anti-TNF and < 5 DMARDs nonresponders	Corticosteroids folate supplementation	MTX + RTM 2 doses vs. MTX + PLB vs. MTX + steroids 2 regimens	465	Phase IIb RCT, DB, multifactorial dose-finding 24+80	ACR 20/50 RTM superior to PLB
supportive	MTX for 6 months at stable dose for 28 days	Corticosteroids NSAIDs	MTX + ABA 10 mg/kg vs. MTX + ABA 2 mg/kg vs. MTX + PLB	339	Phase II B RCT, DB, dose ranging 24	10 mg superior to PLB
Abatacept [26]	Inadequate response to MTX.	Corticosteroids	MTX + ABA vs. MTX + PLB	652	Phase III RCT, DB, 24	ACR 20 at 6 months disability index and erosion score at 12 months ABA + MTX superior to MTX
pivotal	MTX for 3 months at stable dose for 28 days	Corticosteroids	any nonbiologic treatment or ANK + ABA vs. any nonbiologic treatment or ANK + PLB	391	Phase III, RCT, DB 24	ACR 20, disability index significantly superior to PLB
Phase IIB exploratory	Anti-TNF inadequate response ETN: 28 days washout IFX: 60 days washout	Low-dose stable corticosteroids stable NSAIDs	ETN + ABA vs. ETN + PLB	121	Phase IIB RCT, DB, PG 48	Poor tolerability and poor adherence to combination treatment
Supportive safety assessment	Inadequate response to etanercept	Low-dose stable corticosteroids stable NSAIDs	nonbiologic or biologic DMARDs or combination + ABA vs. nonbiologic or biologic DMARDs or combination + PLB	1441	Phase III RCT, DB, 52	Data not sufficient to support the use of ABA with other DMARDs other than MTX
pivotal	Active RA with/without comorbidities, background DMARDs and/or biologics stable for 3 months	Folate, low-dose stable corticosteroids, stable NSAIDs	MTX + ABA vs. MTX + PLB vs. MTX + IFX	748	Phase III RCT, DB, 24	DAS 28 scores: ABA and IFX $p < 0.001$ vs. PLB
	Inadequate responders to MTX.					
	Stable MTX, other DMARDs not permitted					

A new drug, B active comparator, PLB placebo, *tw* twice weekly, *eow* every other week. See abbreviation list for all other definitions

Table 2 Designs adopted in registration trials and approved indications of each antirheumatic drug

Drug	A vs. PLB	A vs. B (vs. PLB)	A vs. B vs. A + B	A + B vs. B + PLB	Add-on A + PLB A + B	Approved indication
leflunomide		4				Treatment of adults with active RA as a DMARD
etanercept	2	1	1		2	In combination with MTX for moderate to severe active RA in adults with inadequate response to DMARDs
infliximab				1	1	In combination with MTX for reduction of signs and symptoms and improvement of physical function in active RA patients with inadequate response to DMARDs. Patients with severe, active progressive disease not previously treated with MTX or DMARDs
adalimumab	2		1		2	In combination with MTX for moderate to severe active RA in adults with inadequate response to DMARDs and in patients with severe, active progressive disease not previously treated with MTX. In monotherapy in case of intolerance to MTX or continued treatment with MTX is inappropriate
anakinra					2	For signs and symptoms of RA in combination with MTX in patients with an inadequate response to MTX alone
rituximab			1		2	In combination with MTX for treatment of adults with severe active RA with inadequate response or intolerance to other DMARDs including one or more TNF inhibitors
abatacept					6	In combination with MTX for moderate to severe active RA with insufficient response or intolerance to other DMARDs including at least one TNF inhibitor

A new drug, *B* active comparator, *PLB* placebo. See abbreviation list for all other definitions

were no better than established comparators. Four studies (ETN, ADL, RTM, IFX) comparing the efficacy of the test products and of the active comparator MTX alone or their combinations confirmed the better efficacy of the combination arm.

The add-on design was the most frequent approach used in the approval process of new biologic response modifiers. Three strategies were used in combination therapy in RA: “parallel” (multiple treatments are administered concurrently), “step-up” (addition of a DMARD to the background of another, partially effective, DMARD) and “step-down” (concomitant DMARDs sequentially withdrawn once benefit has been achieved) [27]. For four agents (IFX, ETN, ADL and RTM) the add-on trials contributed to obtaining approval as combination therapy, whereas ANK and ABA were authorised only on the data of add-on trials.

The new biologic agents are all indicated (Table 2) in combination with MTX for treating adult patients with active RA inadequately responding to previous DMARDs, including MTX and one or more TNF inhibitors, such as RTM and ABA. ADL is approved for monotherapy only in case of intolerance to MTX or when continued treatment with MTX is inappropriate.

A further critical issue in the process of approval of new agents is pharmacokinetic drug interactions. Table 3 summarises the pharmacokinetic and interaction studies reported in the EPAR. Routine pharmacokinetic studies were produced for each new agent, but formal studies on interactions were either generally limited (MTX raised

plasma concentrations of IFX, did not modify the kinetics of RTM and ETN; the influence of ETN on MTX was not investigated) or neglected, as in the case of concomitant background therapy. Only clinical evidence of toxicity in patients concurrently receiving two TNF antagonists led to the warning not to use such combinations.

Discussion

Our survey found that add-on trials had an important role in the approval process of the newer antirheumatic agents, possibly because this approach easily provides a demonstration of efficacy. In the last few years, the comparison of a new drug or placebo added to ongoing DMARD treatment has become the standard trial design, with MTX being the standard DMARD [28, 29], in a population of so-called partial responders.

Add-on trials are reported to have some practical advantages (absence of flares, similarity to daily practice, benefits of maintenance of concomitant drugs, proof of concept accepted by regulatory agencies). However, data on the superiority of combination DMARD therapy in RA are controversial [30] because of confounding factors. These include inadequate definition of incomplete responders to previous/concomitant DMARDs, quite low percentages of patients without adequate response to MTX and background therapy (NSAIDs, glucocorticoids) not considered a part of the add-on combination [31–33].

Table 3 Pharmacokinetics (PK) and interaction studies for each antirheumatic drug

drug	pharmacokinetic studies	interaction studies	warnings
leflunomide	Basic parameters Impaired renal function, no change Impaired liver function, not done but contraindicated	No influence by CYP inhibition or induction (cimetidine, rifampicin). No safety problems with NSAIDs No effect on PK by cimetidine, ibuprofen, diclofenac No PK interaction with MTX	Liver and renal impairment contraindicated Concomitant administration of hepatotoxic or hematotoxic DMARDs (MTX) not advisable
infliximab	Basic parameters No studies on metabolism and excretion No impaired organ function studies	MTX slightly raised IFX plasma concentrations	The combination with ANK and ETN (serious infections seen in clinical studies) not recommended
etanercept	Basic parameters Renal and hepatic failure (limited data): No change in dosage No effect of age, gender, ethnic origin PK in CHF patients similar to healthy subjects and RA patients	No formal studies conducted No interactions observed in clinical trials PK not altered by MTX No data on the effect of ETN on MTX (no effect in animal studies)	The combination with ANK not recommended (serious infections seen in clinical studies)
adalimumab	Basic parameters No data on renal, hepatic failure CI 44% lower in MTX-treated patients Trend to decreasing CI with increasing age. No gender differences.	Concomitant NSAIDs: no influence on safety Limited experience on concomitant DMARDs other than MTX MTX increased exposure to ADL by about 40% Slightly higher % of infectious SAEs in ADL patients taking corticosteroids	The combination with ANK not recommended (serious infections seen in clinical studies)
anakinra	Basic parameters subcutaneous and intravenous injection. Elimination route not studied. CI: no effect of gender or age; reduced in hepatic impairment; no studies in severe insufficiency	No evidence of interactions with NSAIDs or corticosteroids (no studies)	Not to be used in severe renal insufficiency Combination with any other TNF antagonist not recommended (increased risk of serious infections)
rituximab	Basic parameters No data on renal, hepatic failure and hyproproteinuria No data on PK of NSAIDs or other drugs	No specific studies. Not influenced by cyclophosphamide or MTX. Cmax may be increased by high doses of corticosteroids.	Concomitant/sequential use of other DMARDs other than those specified under RA indications not recommended Insufficient data on safety of sequential use of other DMARDs (including TNF inhibitors)
abatacept	In RCT phase II/III basic parameters. No accumulation following monthly dosing. No effect of age or renal function. No studies in special populations	No specific studies. In phase III co-administered MTX, corticosteroids, NSAIDs, anti-TNF no influence on ABA CI.	Combination with TNF antagonists not recommended (increased risk of serious infections)

Some of the drawbacks reported in the literature show up in the add-on studies included in this review (Table 1). The inclusion criteria of the add-on trials submitted to the EMEA show the heterogeneity of the patient populations enrolled (suboptimal response to one or more DMARD, duration, type and dosages of background therapy, with or without washout period, etc.). In the majority of the add-on trials, patients had very active disease and were “inadequate” or “partial” responders to MTX or anti-TNF agents. Another point for concern is the failure to report detailed information about the number and dosage and possible interactions of concomitant background medications, specifically NSAIDs and corticosteroids, which are anti-inflammatory agents with their own efficacy and toxicity. Another disadvantage of this design is that it can be potentially harmful, as shown by the negative experience with combined ANK and ETN [34] and the exploratory phase IIB study adding ABA to ETN [35].

The main concern, however, regards the use of placebo in patients with a poor response to current treatment. If the treatment is definitively ineffective, it should not be continued in either treatment group, as it would be useless and therefore unethical. If it is partially effective, adding placebo in one arm while providing an active drug in the other would be unethical too. It is advisable in any case to compare two active treatments, as either an alternative or an add-on to the current unsatisfactory therapies. Comparing one treatment against two seems an uneven challenge, it being possibly easier for the new drug together with the standard treatment to perform better than the latter alone. Moreover, this approach does not provide adequate information on how the test drug added on top of ongoing therapies fares in comparison with other treatments.

The lack of direct comparisons between new active principles makes it difficult to choose among so many alternatives. Ideally, it would be useful to compare any new agent with the best current treatment and with their combination (A vs. B vs. A + B, than A vs. C vs. A + C, and so on). In view of the lack of direct comparisons of newly approved anti-RA, it is difficult to identify the “gold standard” of treatment on top of MTX with which a new compound should be compared. From a historical point of view, the first approved agent, LFE, should have served as comparator for the next ones, namely IFX and ETN. Combinations should also be compared with each other. In the approval process, the true value of the new agent alone and in combination should be assessed through superiority clinical trials.

The pharmacokinetic drug interactions studies, which do not actually seem to be considered very important, are in fact needed because research on interactions could be

helpful in developing rational combination therapy with less toxicity. These studies would also show whether apparently better efficacy of the add-on approach is merely due to a higher concentration of one or the other component of the combination.

In conclusion, the add-on approach is popular for registration purposes, as it offers many practical, financial (savings in time and investment and exempting the sponsor from correct comparisons) and theoretical advantages, mirrors clinical practice and substantially demonstrates the efficacy of a combination. This design, however, does not provide firm proof that any effect observed really relates to the combination, as the control arm is so often a placebo in patients with active disease despite treatment with MTX or other background therapy, so it is difficult to assess the intrinsic efficacy and safety of the new agent and its value as an alternative to current remedies. The indications granted do not indicate whether newer drugs can replace standard treatments in nonresponders and even less whether they can do better. Nor do they say which of them must come first, if any.

This review of the clinical data submitted to the EMEA indicates that to obtain approval easily, no comparative studies between the new biologic anti-RA agents were done, even though efficacy patterns seem to be similar and a direct comparison would have been possible, at least after the MA. Surprisingly, not even equivalence or noninferiority trials against the best available treatment were done. As uncontrolled trials artificially set up in the late stages of diseases, placebo-controlled trials and equivalence or noninferiority trials, the add-on approach complies with the European Pharma law [36], which allows each drug to be approved on the basis of its own quality, safety and efficacy, with no need for comparison with active comparators. Legislators and regulatory authorities could usefully redesign regulations and registration trial requirements, as suggested above, with a view to obtaining unequivocal data about the comparative efficacy and safety of current and newer drugs, including anti-RA agents, which would best meet the needs of the clinical community.

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