Editorial

Updating the 2003 European regulatory requirements for registering disease-modifying drugs to be used in the treatment of rheumatoid arthritis

EMA guidelines: out of date

Pivotal clinical trials of several drugs licensed in Europe have used the 'Points to consider on clinical investigation of medicinal products other than NSAIDs for the treatment of rheumatoid arthritis', published in 2003 by the European Medicines Agency's (EMA) Committee for Proprietary Medicinal Products for Human Use (CPMP) [1].

This document was produced to specify requirements for investigation and approval of new DMARDs; however, since it was published we have seen the development of novel therapies for RA (especially biologic agents) and new therapeutic strategies emphasizing early intervention and tight control to achieve low disease activity or remission [2]. In light of this, the ethics and study design of clinical trials need to be reassessed.

To address this situation, the authors—a consensus committee bringing together expertise in RA, clinical trial design and regulatory affairs—reviewed the current literature. A consensus was reached, endorsed by all authors, that updates the CHMP guidance, specifically as it relates to, the choice of comparator in different patient populations, the assessment of signs and symptoms and physical function and structural damage evaluation and duration of trials.

Patient populations

The patient population studied will have an important influence on the choice of comparator, but also on the assessment of joint damage. Three distinct RA populations can be defined readily by prior treatment, implying three potential indications for use of a new agent: (i) DMARDnaïve, including MTX-naïve, patients (first-line indication); (ii) MTX-refractory or MTX-intolerant patients (second-line indication); and (iii) biologics-refractory or biologicsintolerant patients who have failed one or more biologics (third-line indication). While the target of RA therapy today generally constitutes remission or low disease activity [2], different aims need to be considered for each of these patient populations. It is important to optimize comparability between studies and to homogenize patient populations by clearly pre-specifying, justifying and documenting failure of or intolerance to previous treatment in the protocol.

Choice of comparator

Early, DMARD-naïve RA (first-line indication)

In early RA or DMARD/MTX-naïve patients, using stateof-the-art therapy to prevent structural damage and irreversible disability is pivotal. It follows that it is unacceptable to study these patients with pure placebo, since joint destruction starts within the first 2 years in 70% of patients [3]. Indeed, most contemporary randomized controlled trials (RCTs) in early RA have employed an active comparator, usually a synthetic DMARD (MTX) [4]. In DMARD- or MTX-naïve RA patients, even those with severe active disease, MTX is still considered the gold standard [5]. Clearly, this is the preferred trial design for this patient population.

A new agent may receive a first-line therapy indication either as monotherapy or in combination with MTX or other DMARDs. First-line monotherapy (or combination therapy) approval might be achieved following a direct comparison of the new agent to MTX, or alternatively to SSZ or LEF, at contemporary doses. The new agent would need to demonstrate statistically significant efficacy that is at least equal to that of MTX/DMARD in terms of signs and symptoms, structural damage and physical function, along with a similar or better safety profile [6].

Established RA

In contrast to early RA, in established RA, new agents have often been evaluated against a placebo comparator, as an add-on to a synthetic DMARD, usually MTX. MTX-refractory RA patients should have demonstrated a documented and auditable inadequate clinical response to previous MTX therapy of at least 4 months duration, with a dose of \sim 25 mg for at least 2 months, unless intolerant [7].

Current CHMP guidance states that continuing placebo treatment indefinitely is unethical; it defines 3–6 months as an acceptable period of use and recommends predefined rules for withdrawal [1]. When continuing prior DMARD therapy, escape rules of 14–16 weeks with primary endpoint analyses at time points before or after the escape have been used by several regulatory trials of licensed EDITORIAL

targeted biologicals [8]. However, the most recent recommendations on RA care [5] indirectly suggest that escape rules should allow for an early escape, namely at 3 months. In this scenario, the new agent would need to demonstrate superior efficacy to placebo in signs and symptoms, but ideally also structural damage or physical function already at 3 months), with at least non-inferiority in these other two. After 3 months, the comparator arm could be switched to, or receive as add-on, another drug licensed for the treatment of RA, in order to continue evaluation of the new agent's comparative safety and maintenance of efficacy in the long term. Further suggestions with maintenance of prognostic balance have also been made [9]. Alternatively, the comparator group could be re-randomized at 3 months to either another standard active treatment (e.g. a licensed biologic or synthetic DMARD) or the new agent.

An active comparator [10], rather than placebo, is more in line with the present standard of care in this RA population. There is still a lack of good RCTs on head-to-head comparisons of biologic agents and it could be suggested that for approval of a biologic agent, comparative trials vs other biologicals should be a requirement. A Phase III study of the new agent plus or minus a synthetic DMARD vs a TNF inhibitor plus synthetic DMARD is highly advised. The TNF inhibitors with MTX are considered the best comparators as they show the tightest confidence intervals for efficacy, have the longest safety record of the targeted biologics and comprise multiple established licensed agents with similar efficacy and safety findings.

However, designing such comparative studies may prove challenging. Observed differences between a new agent and a TNF inhibitor are likely to be small, which may make results difficult to interpret. Furthermore, the potential need for a very large sample size to demonstrate non-inferiority is a recognized obstacle to study conduct.

Biologics-refractory patients

Biologics-refractory RA patients should have demonstrated a documented and auditable inadequate clinical response to previous TNF inhibitor/synthetic DMARD combination therapy of at least 3 months duration before entering a new study. Studies could be designed against a background DMARD such as MTX plus placebo (for 3 months) or the prior biologic therapy, unchanged upon enrolment into the study. The new agent would need to demonstrate superior efficacy to the comparator in signs and symptoms, ideally also structural damage and/or physical function, at 3 months without inferiority in the other assessed variables. After 3 months, to demonstrate maintenance of benefit with the new agent, comparators could be other licensed biologics or synthetic DMARDs that the patients had not previously received.

For a structural damage indication, studies shorter than those specified by the CHMP's 2003 document appear appropriate [11]. To obtain a structural damage claim, randomized, double-blind studies could be conducted against an appropriate comparator for 3 months. To minimize patient exposure to inadequate therapy (placebo with background DMARD), the requirement to confirm short-term structural damage changes with longer term follow-up could also be addressed by instituting another licensed agent at the 3-month limit in all patients in the comparator group (or by re-randomizing). In the comparator group, imputation of the 3-month changes towards ≥ 6 months could be and has been done successfully [12]. In this scenario, all patients would receive X-rays at the 3-month time point of escape and at different time points up to 12 months (or more) for comparative purposes.

While many patients, even with active disease, do not progress within 1 year [13], any early difference (i.e. more rapid progression in the placebo/control group) is likely to be retained at later time points since rescue is limited to the most severe patients. With this design, all patients receive active treatment after 3 months, hence may show a subsequent slowing of the rate of progression. For the original active treatment group, maintenance of the effect seen at 3 months can be documented by within-group comparisons with the results seen at 6 and 12 months. Failure to show a structural benefit at 3 months, as possibly seen with agents with slower onset of effect, should not preclude a structural damage indication if such efficacy is clearly shown at subsequent time points. Importantly, an open-label trial should still be able to lead to a structural claim as long as the radiographs are read blindly.

Regarding assessment of physical function it needs to be borne in mind that long-standing disease refractory to several agents will have a lower responsiveness of disability scores [14] due to accrued joint damage and established, irreversible disability. Thus, under these circumstances, primary endpoints require careful selection. Otherwise, improvement in physical function can already easily be definitely seen from 3 months onward and frequently earlier. Table 1 summarizes the suggestions of the Consensus Group.

The question of endpoints is of particular importance. ACR20/50/70 responder rates have withstood the trends in time, but European League Against Rheumatism (EULAR) and ACR have recently defined the items that should be reported in clinical trials, including publications on clinical trials, in order to ensure better indirect comparability [15, 16]. To this end, the composite scores recommended, aside from ACR response, are DAS-28 joint count, simplified disease activity index (SDAI) and clinical disease activity index (CDAI). In addition, ACR and EULAR have defined new remission criteria [17]. Since remission and low disease activity are current therapeutic goals, these states (rather than responses alone) should constitute clinical trial endpoints [15, 16].

The 2010 ACR/EULAR criteria for RA [18, 19] allow for earlier classification of the disease than the 1987 criteria [20]. Since all clinical trials of the past two decades have employed the 1987 criteria, classification according to both criteria sets should be reported and sub-analyses

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		Current CHN	1P guidance		New sug	gestion
	Time po	ints, months	ſ	Time point	ts, months	
Specific claim	Controlled	Open label ^a	Instruments	Controlled	Open label ^a	Instruments
Disease activity (signs and symptoms)	3–6 ^b	NA	ACR response, Paulus, DAS/ DAS-28 including EULAR reponse	m	0-3 ^b	ACR response, DAS/DAS-28 including EULAR response, SDAI, CDAI, ACR/EULAR remission
Joint damage	12	12	Sharp score including modifica- tions. Larsen score	c	о _с	Sharp score including modifi- cations. Larsen score
Physical function	12	12	HAQ, AIMS (function and quality of life), SF-36 (PCS, PF)	ო	6	HAQ, AIMS (function and quality of life), SF-36 (PCS, PF)
¹ Subsequent to the con	itrolled phase. ^t	^o Usually, more profoun	d response rates (such as ACR50 and	ACR70 or remissi	on) peak later than	the 3-month time point. For safety

a wran or at least 12 months of physical function domain; SF-36: a total PF: to provide physical component summary; combination with the controlled period of study would be required 6 months from baseline. NA: not applicable; PCS: e. .⊑ period time point, assessment 3-month an additional open-label cIncludes assessment at the 36-item health survey assessments, evaluation. short-form

of results according to both presented to ensure comparability with previous trials. Further, it is to be expected that non-radiological imaging modalities, such as MRI or sonography, will soon be sufficiently validated in relation to reproducibility, sopritivity to change and offects on long.

ography, will soon be sufficiently validated in relation to reproducibility, sensitivity to change and effects on longterm clinical and functional outcomes to allow for their use as outcomes in clinical trials. Moreover, in the not too distant future it may become possible to predict the occurrence of RA and the question will arise whether pre-emptive therapy (prevention of occurrence of RA) should be considered. However, these issues need not be addressed today but rather in a subsequent update of the document.

In summary, the recent availability of several powerful drugs and the present recommendations on RA management mean that RA patients' exposure to placebo must be abandoned or at least limited to a very short period, and encourage direct comparisons with active drugs, including face-to-face comparisons between biologics. Strategies to support efficacy claims, including structure, can be proposed to shorten placebo exposure to a maximum of 3 months or to enable the use of an active comparator, in accordance with modern ethical requirements.

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