FRESH FROM THE PIPELINE

Vernakalant

Dobromir Dobrev, Bashar Hamad and Peter Kirkpatrick

In September 2010, vernakalant (Brinavess; Cardiome/Merck) was granted marketing authorization by the European Commission for the rapid conversion of recent-onset atrial fibrillation to sinus rhythm.

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting millions of people worldwide, and its prevalence is expected to increase owing to factors such as the growing aged population¹. Its effects range from symptoms such as breathlessness and chest pain to potentially fatal complications such as stroke^{1,2}.

To reduce the risk of stroke, patients with AF are often treated with anticoagulants and with drugs that control heart rate, such as β -adrenoceptor antagonists^{1,2}. Restoration and maintenance of sinus rhythm is also a major approach for the management of AF^{1,2}. However, established drugs for achieving this goal are limited by either modest efficacy and/or side effects, such as life-threatening ventricular pro-arrhythmias or severe extracardiac toxicities^{1,2}. For example, amiodarone, which is generally considered to be the most effective drug for the treatment of AF and has low pro-arrhythmic potential, is associated with serious systemic side effects¹. In 2009, a derivative of amiodarone that was developed with the aim of overcoming these limitations, dronedarone (Multaq; Sanofi–Aventis), was approved for AF, although it might not be as effective as amiodarone in maintaining sinus rhythm^{1,2}.

Basis of discovery

Many drugs used for the treatment of AF affect ion channels in both atrial and ventricular tissue, and this lack of selectivity means that they are associated with a risk of ventricular pro-arrhythmias¹. Vernakalant was discovered through a search for atrial-selective agents in a canine model of AF^{1,3}.

Drug properties

Vernakalant (FIG. 1) is an anti-arrhythmic agent that affects cardiac Na^+ and K^+ currents, including the atrial-selective currents I_{Kur} and $I_{\text{K}_{\text{ACh}}}$ (REFS 4–6). In animal models of AF and in initial clinical studies, vernakalant significantly prolonged the atrial refractory period without significantly affecting ventricular refractoriness^{4–6}.

Clinical data

The efficacy and safety of vernakalant for the treatment of patients with AF has been assessed in three randomized, double-blind, placebo-controlled studies (known as ACT I, ACT II and ACT III) and in an active comparator trial versus intravenous amiodarone (known as AVRO)^{6–8}. In all of these studies, vernakalant was administered by a 10 minute intravenous infusion at a dose of 3 mg per kg followed by a second 10 minute infusion at a dose of 2 mg per kg 15 minutes later if AF had not been terminated^{6–8}.

The ACT I and ACT III trials investigated vernakalant in the treatment of patients with sustained AF (duration >3 hours, but not more than 45 days)^{6,7}. The primary end point in both trials was the proportion of patients with short-duration AF (3 hours to 7 days) who had treatment-induced conversion of AF to sinus rhythm (cardioversion) for at least 1 minute within 90 minutes of treatment infusion^{6,7}. A secondary efficacy end point was conversion of AF in patients with longer-duration AF (>7 days and ≤ 45 days)^{6,7}.

Treatment with vernakalant effectively converted AF to sinus rhythm compared with placebo^{6,7}. The primary end point was met in 74 out of 145 (51.0%) of patients receiving vernakalant compared with 3 out of 75 (4.0%) of patients receiving placebo in the ACT I study^{6,7}, and in 44 out of 86 (51.2%)

of patients receiving vernakalant compared with 3 out of 84 (3.6%) of patients receiving placebo in the ACT III study⁶. Conversion of AF to sinus rhythm occurred rapidly (the median time to conversion in responders was 10 minutes from the start of the first infusion) and sinus rhythm was maintained over 24 hours (97%)⁶. Vernakalant provided relief of the symptoms of AF consistent with conversion to sinus rhythm⁶.

No significant differences in safety or effectiveness were observed based on age, gender, use of rate-control drugs, use of anti-arrhythmic drugs, use of the anticoagulant warfarin, history of ischaemic heart disease or renal impairment⁶. Assessment of the conversion of AF in patients with longer-duration AF in a total of 185 patients did not show statistically significant differences between vernakalant and placebo⁶.

The ACT II trial investigated the effect of vernakalant in 150 patients with sustained AF (3–72 hours duration) that occurred between 24 hours and 7 days after coronary artery bypass graft and/or valvular surgery^{6,8}. The primary end point was the conversion to sinus rhythm within 90 minutes of dosing, which was achieved in 47 out of 100 (47%) patients who received vernakalant compared with 7 out of 50 (14%) patients who received placebo^{6,8}. The median time to conversion was 12 minutes from the start of treatment infusion⁶.

In the AVRO trial, vernakalant was compared with intravenous amiodarone (administered over 2 hours) in 116 patients with recent-onset AF (3–48 hours)⁶. The primary end point was the proportion of patients who achieved sinus rhythm at 90 minutes after initiating treatment⁶. Treatment with vernakalant converted 51.7% of patients to sinus rhythm at 90 minutes compared with 5.2% of patients treated with amiodarone⁶.

Indications

Vernakalant is approved by the European Commission for the rapid conversion of recent-onset AF (≤ 7 days duration for non-surgery patients, and ≤ 3 days duration for post-cardiac surgery patients) to sinus rhythm in adults⁶.

Figure 1 | **Structure of vernakalant.**

ANALYSIS | ATRIAL FIBRILLATION

- Analysing clinical issues in the treatment of AF is Dobromir Dobrev, M.D., Professor and Chair, Division of Experimental Cardiology, Medical Faculty Mannheim, University of Heidelberg, Germany.

Current pharmacotherapy for AF has major limitations, including moderate efficacy and unpredictable risks of life-threatening pro-arrhythmia with anti-arrhythmic drugs, and bleeding complications with anticoagulants¹. Non-pharmacological (ablation) approaches have improved, but still have safety and efficacy limitations, and are not applicable for a substantial proportion of the AF patient population.

These considerations and the growing importance of AF as a clinical problem have fostered efforts to develop anti-arrhythmic drugs with improved efficacy and safety profiles, focusing on favourable multichannel-blocking profiles, atrial-specific currents such as $I_{K_{ACh}}$ and I_{Kur} , and atrial-selective Na^+ -channel blockade. Molecular modification of the highly effective multichannel-blocker amiodarone to improve safety and tolerability led to dronedarone, which is the first anti-arrhythmic drug that reduces cardiovascular mortality and hospitalization of patients with AF². However, dronedarone was approved for the suppression of AF, but not for the reduction of cardiovascular mortality in patients with AF.

Vernakalant is the first atrial-selective drug to reach the market. Atrial-selectivity of vernakalant is achieved by inhibiting $I_{K_{ACh}}$ and I_{Kur} and by exploiting state-selective rapidly unbinding Na^+ channel-inhibitory properties that produce stronger effects on atrial than ventricular action potentials, especially during rapid rhythms like AF. Consequently, vernakalant is associated with a low pro-arrhythmic risk for ventricular tachyarrhythmias. Owing to its very short half-life, vernakalant has primarily been used intravenously for termination of recent-onset AF, but a longer-acting slow-release oral formulation is in clinical trials.

The efficacy of vernakalant for acute AF termination seems comparable with other available compounds⁹, although comparative studies have not been conducted. Although the AVRO trial compared intravenous vernakalant with amiodarone in recent-onset AF⁶, amiodarone is less suitable for acute AF cardioversion¹⁰ because of its slow (up to 24 hour) onset of action, and thus is not the most appropriate comparator when assessing the short-term (90 minutes) success rate of pharmacological cardioversion. Head-to-head trials with intravenous flecainide (not available in North America) are needed to validate the superiority of vernakalant for acute AF cardioversion in the different patient populations. Of note, vernakalant

has a substantially lower AF conversion rate in congestive heart failure (26.9%) than in haemodynamically stable patients (54.1%)^{6–8}, suggesting that vernakalant is safe but less effective in patients with structural heart disease. Vernakalant was also not found to be effective in converting typical primary atrial flutter to sinus rhythm⁶, and so cannot replace established drugs used for the acute termination of atrial flutter, such as ibutilide and dofetilide. Finally, the clinical value of vernakalant for prevention of AF recurrence requires further large-scale trials with suitable AF patient populations.

Overall, given the atrial selectivity and different safety profile of vernakalant, it provides an important addition to the options for anti-arrhythmic pharmacotherapy, with the potential to change the algorithm for acute AF cardioversion.

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Box 1 | The market for drugs for atrial fibrillation

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The global market for anti-arrhythmic agents was worth ~US\$1.57 billion in the period June 2009 to June 2010, with 10% growth compared with the previous 12-month period¹¹. Amiodarone, which is available in generic versions, dominated this market, with sales of \$442 million (a 28% share), followed by propafenone (17% share) and flecainide (16% share), which also have generic versions available¹¹. The growth was mainly fuelled by the launch of dronedarone (Multaq; Sanofi–Aventis), which had 12-month sales of \$121 million and 8% market share just 1 year after launch¹¹.

In September 2010, intravenous vernakalant (Brinavess; Cardiome/Merck) was granted marketing approval in the European Union, Iceland and Norway for the conversion of recent-onset atrial fibrillation (AF) to sinus rhythm in adults. The drug is also being developed as a controlled-release oral formulation, which has completed Phase II trials. The market for intravenous anti-arrhythmic agents is only 10% of the total market; the largest market opportunity for vernakalant is for the oral version, which is intended for an indication of normal heart rhythm maintenance and prevention of attacks in patients with AF, competing with dronedarone.

Cardiome has a separate partnership with Astellas Pharma on intravenous vernakalant in the United States. A regulatory application for the acute conversion of AF was filed with the FDA in 2006, and an approvable letter was received in 2008. In August 2009, Cardiome and Astellas agreed to a special protocol assessment with the FDA for a 450-patient Phase III study (ACT 5) for intravenous vernakalant in patients with recent-onset symptomatic AF who do not have a history of heart failure. However, in October 2010, patient enrolment in the trial was suspended following a single unexpected serious adverse event of cardiogenic shock, pending assessment by the FDA. High-end estimates of sales of intravenous vernakalant are \$200 million in 2015 and \$1.1 billion for the oral formulation in 2018 (REFS 12,13).

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Competing interest statement

The authors declare no competing financial interests.