

Julio Pascual  
Hans-Christoph Diener  
Hélène Massiou

## Value of postmarketing surveillance studies in achieving a complete picture of antimigraine agents: using almotriptan as an example

Received: 11 November 2005  
Accepted in revised form: 13 December 2005  
Published online: 31 January 2006

J. Pascual (✉)  
Service of Neurology,  
University Hospital,  
Salamanca, Spain  
e-mail: juliopascual@telefonica.net  
Tel.: +34-923-291100

H.-C. Diener  
University of Essen,  
Essen, Germany

H. Massiou  
Service de Neurologie,  
Hôpital Lariboisière,  
Paris, France

**Abstract** Randomised controlled trials cannot collect all the data relevant for use in everyday clinical practice because drug exposure is limited, endpoints are restricted and some patient populations are excluded. Postmarketing surveillance (PS) studies can add important information for real-world clinical practice. Acute migraine therapy with almotriptan 12.5 mg was evaluated in 4 PS studies, 2 conducted in Spain, 1 in Germany and 1 in France. Almotriptan was associated with a high rate of treatment response and was well tolerated in all 4 studies. In the Spanish and German studies, 2-hour pain-relief, 2-hour pain-free, and sustained pain-free rates were enhanced when patients treated mild pain. Patient

satisfaction with almotriptan, assessed in the German and French studies, was high and the majority of patients preferred almotriptan to their previous acute migraine therapy. In conclusion, PS studies augment our knowledge of antimigraine therapy, giving a more complete picture of how such agents work in the general population.

**Keywords** Randomised controlled trials • Postmarketing surveillance • Triptans • Migraine

### Introduction

Triptans, 5-HT<sub>1B/1D</sub> agonists, have been recognised by both migraineurs and headache specialists as the treatment of choice for acute migraine therapy [1, 2]. Currently there are 7 available triptans, all of which have been studied in numerous randomised controlled trials (RCTs) [3–5]. These RCTs have provided essential data on the efficacy and tolerability of triptans compared with placebo, including long-term data and some head-to-head com-

parisons between triptans. Comprehensive, indirect comparative data on triptans are available from a meta-analysis of 53 RCTs [6].

Although the published literature on triptans in RCTs is extensive, RCTs cannot collect all of the data relevant to use in routine clinical practice. Therefore, it should not be automatically assumed that real-world experience with triptans will exactly mirror RCT findings. Postmarketing surveillance (PS) studies can provide important information on the use of triptans in routine clinical practice [7]. This article will review the strengths and limitations of

RCTs and PS studies with reference to triptans and, as an example, will describe the findings from PS studies of almotriptan conducted in Spain, Germany and France.

### The merits of randomised controlled trials and postmarketing surveillance studies of acute treatments for migraine

When clinical data are ranked according to value and importance in evidence-based clinical reviews and treatment guidelines, findings from high-quality RCTs usually receive the highest ranking, along with meta-analyses. The strength of data from such sources is considered greater than that from clinical cohort studies, high-quality epidemiologic studies and case-control studies [8]. The results of RCTs are greatly valued because the protocols are designed to minimise bias through randomisation of patients, blinding of patients and investigators to study treatments, use of control agents, and predefinition of endpoints. In addition, rigorous follow-up is performed to obtain the most complete data set possible from each patient [7]. However, RCTs also have limitations because these protocols impose restrictions on data acquisition. The basic features of RCT and PS study design, provided in Table 1, illustrate these limitations.

Overall, patients have less drug exposure in RCTs compared with PS surveillance studies, particularly if the study drug is a rescue medication or acute therapy. Fewer patients are enrolled in RCTs compared with PS studies, and the use of controls in RCTs decreases the number of patients receiving the drug of interest [7].

Endpoints in RCTs, which are predefined, are usually constrained by requirements for drug registration. For example, many early RCTs of triptans included 2-hour pain relief (2-h PR) as a primary endpoint. The 2-h PR endpoint requires patients to take their medication when headache pain is moderate to severe in intensity so that a

reduction of 2 points on a 4-point headache pain scale (3=severe, 2=moderate, 1=mild and 0=no pain) can be observed [9]. There are several arguments against the use of 2-h PR as a primary endpoint. First, accumulating data, including those from *post hoc* analyses of protocol violators in RCTs of triptans, suggest that triptan efficacy may be optimised by treating when headache pain is mild rather than waiting until it becomes moderate to severe in intensity [10–14]. Second, when using this endpoint, reduction from severe pain to none and from moderate to mild pain are ranked as equivalent treatment responses. Third, this endpoint does not reflect patients' therapeutic goals. Survey data indicate that most migraineurs want acute therapies to provide complete freedom from pain [15, 16]. Finally, the discriminatory power of the 2-h PR endpoint is poor, as shown by the lack of difference in 2-h PR rates between triptans and analgesics in many RCTs [17]. Because they are not constrained by drug registration requirements, PS studies can include a wider variety of endpoints that are meaningful to patients such as measures of satisfaction with therapy.

Of particular note is the difference in the patient populations between RCTs and PS studies. A number of key patient groups often are excluded from RCTs, that is, the elderly, children, those with comorbid conditions, those using concomitant medications and other patients at higher risk for adverse events (AEs). Because migraine affects more women than men, more young and middle-aged adults than other age groups, and more whites than members of other races [18], the population of migraineurs might mistakenly be thought to be homogenous.

In reality, however, migraine affects a wide variety of patients. One reason is that it affects such a large segment of the population, including an estimated 10%–12% of the population of the western world [18, 19]. Another factor contributing to the diversity of the migraineur population is the association of migraine with a variety of comorbid conditions such as other neurologic conditions, affective disorders and rheumatologic diseases [19–23]. An advan-

**Table 1** Properties of randomised controlled trials vs. postmarketing surveillance studies [7]

Parameter	Randomised controlled trial	Postmarketing surveillance study
Randomisation	Yes	No
Blinding	Double-blind	Open-label
Control	Placebo or active	None
Outcome measurement	Predefined	No predefinition (sometimes)
Follow-up	Rigorous	Incomplete
Patients		
Drug exposure	Limited	Large
Number	Limited	Large
Population	Restricted	Diverse

tage to the inclusion of a diverse patient population in PS studies is that it allows for the identification of differences in drug efficacy, tolerability and safety in individuals with different pharmacogenetics, immune systems, drug metabolism and drug-drug interactions [24]. The longer duration of PS studies allows for the detection of rarer AEs and delayed AEs.

A RCT tests the hypothesis that treatment with one active agent is better than treatment with another active agent or placebo. The results will be valid internally, that is, within the context of the trial, if the trial is properly designed and executed. Most well-designed, randomised, double-blind trials with sufficient statistical power will meet the challenge of internal validity. The more common issue complicating the interpretation of RCTs, however, is external validity, that is, can the findings from a trial be extrapolated to the general population of patients with this disorder. Are the patients being treated in this trial similar to the migraine patients outside of this trial with regard to age, gender, race, comorbid disorders, triptan experience and level migraine-associated disability [25]? Does the different level of care provided in this trial (higher number of visits and measurement scales used, review of informed consent documents explaining the benefits and risks of treatment, the existence of a placebo arm) change the study outputs? It may not be appropriate to generalise the results of RCTs for a given drug to the entire population of patients who might use that agent [7]. PS studies, with their more diverse range of participants, may be more likely to meet the standards for external validity.

### Postmarketing surveillance studies conducted in Spain

Two multicentre, open-label, 3-month patients' follow-up observational PS studies that assessed the efficacy and tolerability of acute migraine therapy with almotriptan 12.5 mg were conducted in Spain [26, 27]. These studies had identical protocols except for the patient recruitment sites. The first study enrolled approximately 1000 patients receiving headache therapy from neurologists. The second study included about 2000 patients receiving treatment for headache from primary care physicians (PCPs). In each study, approximately 4000 attacks were treated. Patient demographics were similar in these 2 studies except for a greater frequency of migraine attacks in the group being treated by neurologists and their greater use of prophylactic migraine medications compared to those being treated by PCPs (35.1% vs. 25.3%).

Almotriptan was associated with a high rate of treatment response in both studies (Table 2). The rates for 2-h PR, 2-hour pain free (2-h PF) and sustained pain free (SPF, pain free at 2 h after dosing and no headache recurrence or use of rescue medication for up to 24 h after dosing) were found to be greater in the PCP patient study compared with the neurology patient study. Rates for 2-h PF and SPF were also higher for the PCPs' patients compared with the neurologists' patients when these endpoints were analysed according to headache severity at time of dosing. In both studies, greater response rates were obtained when patients took their medication when headache pain was mild compared with treatment when pain was moderate or severe.

**Table 2** Two-hour pain-relief, 2-hour pain-free and sustained pain-free rates in postmarketing surveillance studies of almotriptan conducted in Spain and Germany

	Pain intensity at time of dosing				
	All attacks	Mild	Moderate/severe	Moderate	Severe
<i>Spanish PS studies</i>					
Neurologists' patients [7, 26, 27]					
2-h PR	65.5				
2-h PF	26.6	59.7	23.3		
SPF	18.6	43.9	16.1		
PCPs' patients [7, 26, 27]					
2-h PR	86.6				
2-h PF	50.5	80.5	48.5		
SPF	44.8	70.9	43.0		
<i>German PS study [7, 28]</i>					
2-h PR	84.5			96.3	74.0
2-h PF	41.5	89.3		55.3	22.1

PS, postmarketing surveillance; 2-h PR, 2-hour pain relief; 2-h PF, 2-hour pain free; SPF, sustained pain free

The overall incidence of AEs reported in these 2 trials was low: 3.9% of patients in the neurologist study and 1.1% in the PCP study. The most commonly reported AEs were somnolence (0.9%), nausea (0.8%) and dizziness (0.7%) in the neurologist study, and nausea (0.4%), abdominal pain (0.2%) and somnolence (0.2%) in the PCP study. Most AEs were mild to moderate in intensity.

### Postmarketing surveillance study conducted in Germany

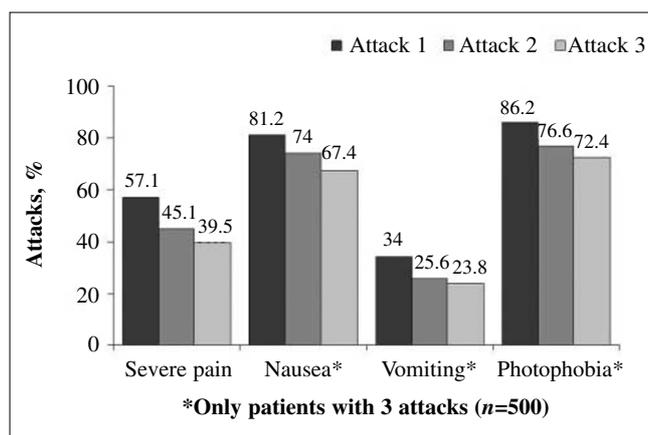
The PS study of almotriptan efficacy and tolerability conducted in Germany was a multicentre, open-label observational study including 899 migraineurs recruited by 307 neurologists and PCPs [28]. Migraineurs who had never used almotriptan received treatment with this agent at a dose of 12.5 mg for up to 3 migraine attacks (preferably consecutive attacks). Data were obtained for the treatment of 2131 attacks, with more than half of the patients treating 3 attacks and about one-quarter treating 2 attacks.

Almotriptan 12.5 mg was associated with a 2-h PR rate of 84.5% and a 2-h PF rate of 41.5% for all attacks (Table 2). Analysis of 2-h PF according to headache intensity at time of treatment showed a much higher rate for treatment when headache pain was mild compared with that for therapy delayed until pain was moderate or severe. Almotriptan treatment was associated with relief from nausea, vomiting and photophobia in greater than 90% of attacks with these associated symptoms.

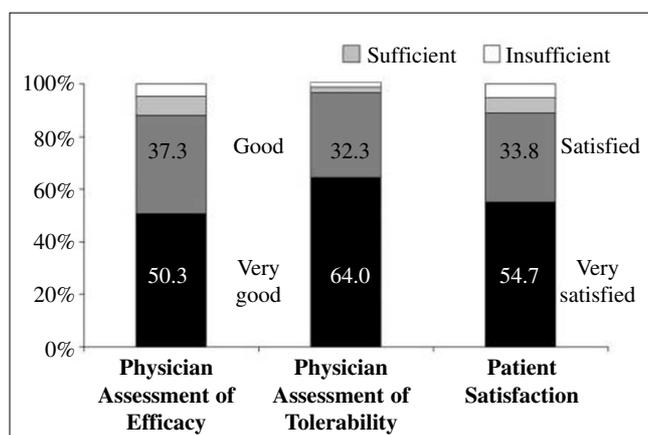
A total of 500 patients provided outcomes for 3 attacks; these data were used to assess consistency of treatment response and baseline intensity of headache pain and other migraine-associated symptoms. Consistency was defined as successful treatment of  $\geq 2$  out of 3 attacks with success referring to a decrease in pain intensity from moderate or severe to mild or none at 2 h after treatment. The consistency rate for almotriptan 12.5 mg was 87.3%, and 69.3% of patients achieved treatment success in 3 out of 3 attacks. Analysis of baseline pain and associated symptoms showed that the intensity of headache pain and symptoms of nausea, vomiting and photophobia at the time of treatment decreased from attack 1 to 3, suggesting that patients learned to treat their migraines earlier (Fig. 1).

The incidence of AEs was 1.1% of patients with a total of 29 events across all 2131 migraine attacks. A total of 21 of the 29 AEs were deemed possibly or probably related to therapy. None of the AEs were serious. The most common AEs were fatigue (0.3% of patients) and nausea (0.2% of patients).

Physicians' global assessment of almotriptan efficacy was "good" or "very good" for 87.6% of the patients (Fig. 2),



**Fig. 1** Intensity of headache pain and migraine-associated symptoms at time of treatment with almotriptan 12.5 mg for 500 patients in the German postmarketing surveillance study for whom data on 3 attacks were available [28]



**Fig. 2** Physicians' global assessment of efficacy and tolerability and patients' overall assessment of treatment satisfaction from the German postmarketing surveillance study [28]

and their global assessment of almotriptan tolerability was "good" or "very good" for 96.3% of patients. Patients' ratings of their satisfaction with treatment were high, with more than half (54.7%) indicating that they were very satisfied with almotriptan and about another one-third (33.8%) stating that they were satisfied with almotriptan. Compared with their previous acute migraine therapies, 80.3% of patients considered almotriptan to be more effective, 13% found no difference between almotriptan and their previous migraine therapy, and 5.1% thought that the previous migraine treatment was better. Analysis according to previous triptan usage showed that almotriptan was preferred by 80.5% of naratriptan users, 73.7% of sumatriptan users, 71.4% of rizatriptan users and 69.8% of zolmitriptan users.

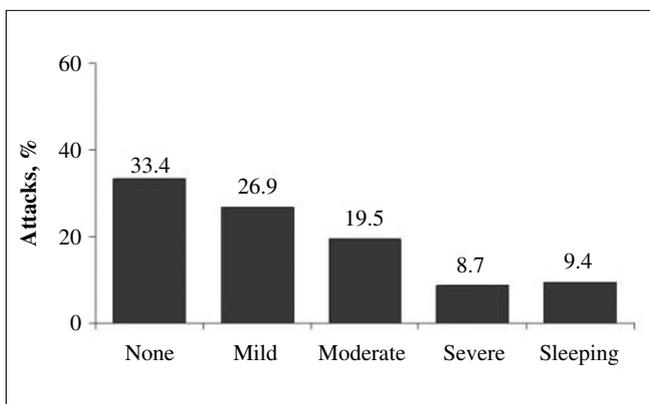
## Postmarketing surveillance study conducted in France: MISTRAL

The MIgraine – Satisfaction with Treatment: Reality with ALmogran (MISTRAL) was an open-label, multicentre study of almotriptan 12.5 mg conducted in France that assessed efficacy, tolerability and patient satisfaction among migraineurs with a long history of migraine who were dissatisfied with their current acute therapy [29]. Data from 434 patients (342 evaluable for efficacy), 57.6% of whom had been using a triptan, were obtained for 929 attacks (up to 3 consecutive attacks/patient) by 154 neurologists. The patients included in the MISTRAL study probably suffered from a more severe disease than the general population of migraineurs, as indicated by the high proportion of patients receiving migraine prophylaxis (34.3%) and their receiving treatment from neurologists rather than PCPs.

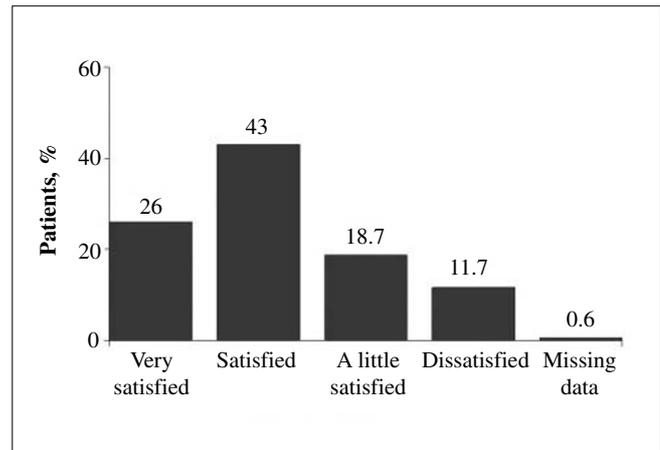
Baseline pain intensity was mild in 15% of attacks, moderate in 50% and severe in 35%. At 2 hours after treatment, headache pain had disappeared in 33.4% of attacks, was mild in 26.9%, moderate in 19.5% and severe in 8.7% (9.4% of patients were asleep at this point) (Fig. 3). The rate of pain relief was 69.3%, the recurrence rate (within 24 h) was 28.4% and emergency analgesics were used in 20.9% of attacks by 32.6% of patients.

AEs were reported by 29.8% of patients. The most common AEs were nausea (8.5%), fatigue (6.4%) and somnolence (5.8%). Treatment-related AEs occurred in 23.7% of patients. The rate of AE-related discontinuation was 2.6% of patients.

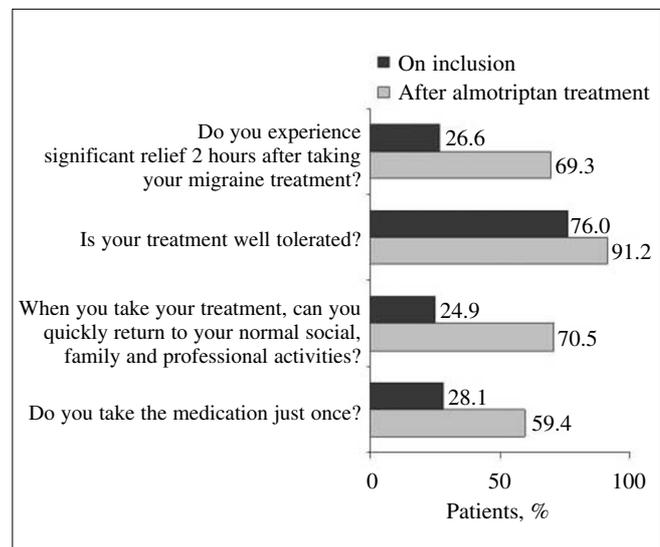
Patient satisfaction with almotriptan treatment was high in the MISTRAL study. The proportion of patients who were very satisfied/satisfied overall with therapy was 69% (Fig. 4). Data collected using a 4-item questionnaire developed by the National Agency for Accreditation and Evaluation in Health (ANAES) for determining the need



**Fig. 3** Headache pain intensity 2 h after treatment with almotriptan 12.5 mg in the French postmarketing surveillance study [29]



**Fig. 4** Patients' global satisfaction with treatment with almotriptan 12.5 mg at the study end in the French postmarketing surveillance study [29]



**Fig. 5** Proportion of patients answering “yes” to each of the questions in the National Agency for Accreditation and Evaluation in Health (ANAES) questionnaire at study inclusion and at study end in the French postmarketing surveillance study [29]

to change acute migraine therapy [30] revealed that almotriptan 12.5 mg was associated with an increased proportion of patients experiencing significant relief at 2 h (69.3% vs. 26.6%), tolerating the medication well (91.2% vs. 76.0%), able to rapidly resume normal activities (70.5% vs. 24.9%) and taking only 1 dose (59.4% vs. 28.1%) compared with previous therapies (Fig. 5). At study end, 73.1% of patients had at least 1 additional “Yes” response on the ANAES questionnaire compared to study onset and 40.9% of patients answered “Yes” to all 4 questions; 56.4% of patients expressed a preference for continuing almotriptan therapy.

## Discussion

A variety of different types of trials and analyses are needed to obtain a complete view of the efficacy and tolerability of a given therapeutic agent. Although RCTs provide internally valid data with minimal bias, these studies do not provide all of the information needed for a complete picture of a drug's efficacy and tolerability. PS studies can include endpoints not required for drug registration, collect data on alternative dosing regimens, and enrol patients who might not be eligible for RCTs. As a result, PS studies can add valuable information on real-world clinical experience.

The European PS studies presented here demonstrate that almotriptan was associated with a high rate of treatment response in the community setting. The Spanish and German studies assessed efficacy using the conventional acute migraine therapy endpoint 2-h PR along with 2-h PF and SPF. The 2-h PF and SPF endpoints are highly relevant to migraineurs because they incorporate top-ranked treatment attributes: rapid response, and complete freedom from pain in 2-h PF, and rapid response, complete freedom from pain, and no headache recurrence in SPF [15].

In the Spanish PS studies, 2-h PR, 2-h PF and SPF were higher for patients recruited by PCPs compared with those for patients recruited by neurologists. These findings suggest that patients receiving therapy for migraine from neurologists, who were suffering from more frequent migraine attacks, may be more difficult to treat than those receiving therapy from PCPs. However, the rates for 2-h PR, 2-h PF and SPF observed for the neurologists' patients indicate that almotriptan was efficacious in that population as well.

The Spanish and German PS studies showed that the efficacy of almotriptan was greater when the medication was taken when headache pain was mild compared with treatment delayed until pain was moderate or severe, consistent with retrospective findings from RCTs of almotriptan [11–14]. Findings from the German PS study showed that over 3 attacks there was a tendency to treat headache pain and associated symptoms at increasingly milder intensity on average. This result suggests that patients were learning to recognise and treat migraine during earlier stages.

Although there is increasing recognition that triptans appear to be most efficacious when used during the mild stage of migraine headache pain, patients may be more reluctant to treat mild than moderate or severe pain because of tolerability issues. A survey of greater than 1000 migraineurs found that concern about AEs had caused two-thirds of them to delay or avoid using a prescription medication for migraine [31]. The AE profile of almotriptan, shown in RCTs to be similar to that of placebo [11–14, 32] and validated as “very good” in PS studies, and its demonstrated efficacy for treating migraine headache during the mild stage [11–14, 32], make almotriptan an ideal triptan for early migraine intervention.

Almotriptan was associated with a high level of patient satisfaction in the German and French studies. This was especially noteworthy in the French study as inclusion criteria required patients to be dissatisfied with their current acute therapy. Furthermore, the majority of patients in these studies preferred almotriptan to their previous acute migraine therapy. These findings are consistent with the results of the meta-analysis of 53 RCTs of oral triptans, which showed that on the basis of efficacy, consistency and tolerability, almotriptan 12.5 mg was 1 of 3 triptan doses associated with the greatest likelihood of consistent treatment success [6].

In summary, while RCTs provide the highest levels of quality evidence and the least bias, PS studies provide valuable data on real-world experience with agents such as triptans. They can have greater external validity compared to RCTs as they generally involve a more diverse yet representative segment of the general population of individuals with migraine. PS studies often measure endpoints that are more important to patients, in addition to investigating patient satisfaction and preference. PS studies of almotriptan showed this agent to be efficacious, associated with a high level of patient satisfaction, and well tolerated for the acute treatment of migraine. The efficacy of almotriptan in this setting was greatest when treatment was initiated during mild headache pain. In conclusion, PS studies add to our body of knowledge of antimigraine therapy, giving a more complete picture of how such agents work in real-world settings.

## References

1. Silberstein SD (2000) Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 55:754–762
2. Robbins L (2002) Triptans versus analgesics. *Headache* 42:903–907
3. Diener HC, Kaube H, Limmroth V (1999) Antimigraine drugs. *J Neurol* 246:515–519
4. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine—current understanding and treatment. *N Engl J Med* 346:257–270
5. Silberstein SD (2004) Migraine. *Lancet* 363:381–391

6. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ (2001) Oral triptans (serotonin 5-HT<sub>1B/1D</sub>) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 358:1668–1675
7. Pascual J (2005) Efficacy and tolerability of almotriptan in postmarketing surveillance studies. *Eur Neurol* 53[Suppl 1]:34–40
8. American Academy of Family Physicians (2004) Levels of evidence in AFP. Available at: <http://www.aafp.org/x17444.xml>. Accessed September 26, 2004
9. Edmeads J (2005) Defining response in migraine: which endpoints are important? *Eur Neurol* 53[Suppl 1]:22–28
10. Cady RK, Sheftell F, Lipton RB et al (2000) Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. *Clin Ther* 22:1035–1048
11. Pascual J, Cabarrocas X (2002) Within-patient early versus delayed treatment of migraine attacks with almotriptan: the sooner the better. *Headache* 42:28–31
12. Pascual J (2002) Clinical benefits of early triptan therapy for migraine. *Headache* 42[Suppl 1]:S10–S17
13. Mathew NT (2003) Early intervention with almotriptan improves sustained pain-free response in acute migraine. *Headache* 43:1075–1079
14. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X (2004) Almotriptan improves response rates when treatment is within 1 hour of migraine onset. *Headache* 44:318–322
15. Lipton RB, Hamelsky SW, Dayno JM (2002) What do patients with migraine want from acute migraine treatment? *Headache* 42[Suppl 1]:S3–S9
16. Davies GM, Santanello N, Lipton R (2000) Determinants of patient satisfaction with migraine therapy. *Cephalalgia* 20:554–560
17. Lipton RB, Bigal ME, Goadsby PJ (2004) Double-blind clinical trials of oral triptans vs other classes of acute migraine medication – a review. *Cephalalgia* 24:321–332
18. Breslau N, Rasmussen BK (2001) The impact of migraine: epidemiology, risk factors, and co-morbidities. *Neurology* 56[Suppl 1]:S4–S12
19. Lipton RB, Stewart WF (1998) Migraine headaches: epidemiology and comorbidity. *Clin Neurosci* 5:2–9
20. Breslau N, Merikangas K, Bowden CL (1994) Comorbidity of migraine and major affective disorders. *Neurology* 44[Suppl 7]:S17–S22
21. Joish VN, Cady PS, Bennett DM, Harris RB (2000) An epidemiological case-control study of migraine and its associated comorbid conditions. *Ann Epidemiol* 10:460
22. Shechter AL, Lipton RB, Silberstein SD (2001) Migraine comorbidity. In: Silberstein SD, Lipton RD, Dalessio DJ (eds) *Wolff's headache and other headache pain*. Oxford University Press, New York, pp 108–118
23. Ruoff GE (2004) Migraine comorbidity: consequent pharmacologic strategies for treatment. *Headache Pain* 15:9–15
24. Atuah KN, Hughes D, Pirmohamed M (2004) Clinical pharmacology: special safety considerations in drug development and pharmacovigilance. *Drug Saf* 27:535–554
25. Lipton RB (2001) Studying the migraine studies: methodological issues in comparative trials of acute medications. *Am J Clin Proc* 1:51–57
26. Pascual J, Lainez JM, Leira R et al (2003) Almotriptan in the treatment of migraine attacks in clinical practice: results of the TEA 2000 observational study. *Neurologia* 18:7–17
27. Pascual J, Tranche S, Leira R et al (2003) Almotriptan in clinical practice: experience in primary care vs neurology setting. *Headache* 43:525
28. Diener HC (2005) Consistent efficacy, tolerability, and high levels of satisfaction with almotriptan 12.5 mg when used to treat multiple migraine attacks in routine clinical practice. *Headache* 45:624–631
29. Massiou H, Pradalier A, Donnet A, Lanteri-Minet M, Allaf B (2005) Evaluation of efficacy, tolerability, and treatment satisfaction with almotriptan in 3 consecutive migraine attacks: MIGRAINE – Satisfaction with Treatment: Reality with ALmogran (MISTRAL) study. *Eur Neurol* (*in press*)
30. Geraud G, Lanteri-Minet M, Lucas C, Valade D (2004) French guidelines for the diagnosis and management of migraine in adults and children. *Clin Ther* 26:1305–1318
31. Gallagher RM, Kunkel R (2003) Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. *Headache* 43:36–44
32. Dodick DW (2001) Oral almotriptan in the treatment of migraine: safety and tolerability. *Headache* 41:449–455