J Headache Pain (2004) 5:247–250
DOI 10.1007/s10194-004-0134-1

BRIEF REPORT

Douglas C. McCrory
Paul Williams

Selecting the preferred triptans

Received: 22 January 2004
Accepted in revised form: 26 May 2004

D.C. McCrory (✉)
Duke University Center for Clinical Health Policy Research,
2200 W. Main Street, Suite 220,
Durham, NC 27705, USA
e-mail: douglas.mccrory@duke.edu
Tel.: +1-919-2869225
Fax: +1-919-2865601

P. Williams
PAREXEL International
101-105 Oxford Road,
Uxbridge, Middlesex, UK

Abstract The objective was to identify a subset of preferred triptans from among available agents. A criterion of dominance was applied to statistically significant differences which emerged from a recent meta-analysis of placebo-controlled trials of the oral triptans in the treatment of acute migraine. Three alternatives – almotriptan 12.5 mg, eletriptan 80 mg and rizatriptan 10 mg – emerged as non-dominated. These were not only superior on an individual basis, but, taken as a group, provided statistically significant superiority over the reference product (sumatriptan 100 mg) on all 5 treatment attributes studied. However, one of these, eletriptan 80 mg, is not approved for use as first line treatment, so the subset of preferred triptans for the treatment of acute migraine therefore comprises almotriptan 12.5 mg and rizatriptan 10 mg. Thus, almotriptan 12.5 mg and rizatriptan 10 mg are the preferred agents for the treatment of acute migraine.

Key words Triptans · Migraine · Dominance

Introduction

Migraine affects 303 million individuals worldwide [1]. It disables almost 25% of women and 9% of men [2] in the United States and, in addition to the impact on patients and their families, is also a major burden on the economy. Direct and indirect costs in the United States amount to almost $14 billion per year [3]. Serotonin (5-hydroxytryptamine, 5-HT) plays a critical role in the pathophysiology of migraine, and triptans are 5-$HT_{1B/1D}$ receptor agonists shown to be highly effective in aborting acute migraine attacks [4]. Since the introduction of sumatriptan in 1991, 6 other triptans – almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan – have become available.

Patients' responses to individual triptans can vary, and most physicians treating migraine patients will need more than one triptan in their armamentarium, but developing familiarity with all of the triptans is probably not feasible. At the individual patient level, the appropriate question is, "which is the preferred triptan for this patient?" But at the physician level, the question is more likely to be "which are the preferred triptans for the physician to know well and to use most often?" The same question, "which are the preferred triptans?", is also relevant to formulary decision-makers.

In this paper the issue of identifying the preferred triptans is addressed by applying a dominance criterion to significant differences, which emerged from a recent meta-analysis of the oral triptans.

Methods

The evidence base

Ferrari et al. recently carried out a meta-analysis of 53 double-blind, randomised, placebo-controlled clinical trials of oral triptans in the treatment of acute migraine, involving over 24 000 patients [5]. Table 1 shows the statistically significant findings for 12 oral triptan/dose alternatives, compared with the reference product sumatriptan 100 mg, extracted from the meta-analysis results. In Table 1, "+" indicates that the product was found to be significantly superior, and "–" indicates that it was significantly inferior, to sumatriptan 100 mg on the particular treatment attribute ("=" indicates no significant difference from sumatriptan 100 mg).

The criterion

In this analysis, we use the decision-analytic concept of dominance as the criterion for selecting the preferred alternatives. Yoon et al. stated, "An alternative is dominated if there is another alternative that *excels* it in one or more attributes and *equals* it in the remaining attributes." [6].

Consider 3 triptans (A, B and C). Triptan A and triptan B are equivalent with respect to sustained pain free, consistency of effect and tolerability, but initial relief is greater for triptan B. Triptan B is therefore dominant over, and is therefore preferred to, triptan A. Regardless of how the treatment attributes are prioritised for any given patient, triptan A can never be the superior treatment.

Triptan C, however, is less well tolerated than triptan A, although initial relief is again greater, and they are equivalent on the other treatment attributes. Here, neither triptan dominates the other, as triptan A would be chosen for patients in whom tolerability is more important than initial relief, and triptan C would be better for those in whom initial relief is considered to be more important.

The data in Table 1 were explored from the dominance point of view, in an attempt to identify a subset of nondominated (i.e., preferred) triptans.

Results

The reference product and its equivalents

Table 1 shows that 5 alternatives - eletriptan 40 mg, rizatriptan 5 mg, sumatriptan 50 mg, zolmitriptan 2.5 mg and zolmitriptan 5 mg – are equivalent to the reference product. There are no statistically significant differences between these triptans and sumatriptan 100 mg across the treatment attributes studied. Any alternative dominated by the reference product will also be dominated by these, and these in turn will be dominated by any alternative dominating sumatriptan 100 mg.

Alternatives dominated by the reference product (and equivalents)

Table 1 shows that the reference product and its 5 equivalents dominate sumatriptan 25 mg, which in turn dominates eletriptan 20 mg. Eletriptan 20 mg and sumatriptan 25 mg are therefore not eligible for inclusion in the subset of preferred triptans.

Table 1 Comparison of the efficacy and tolerability measures for the oral triptans *vs*. sumatriptan 100 mg: statistically significant differences [5, 14]

	Pain free 1 h	Pain free 2h	Sustained pain free	Consistency	Tolerability
Almotriptan 12.5 mg	=	=	+	+	+
Eletriptan 20 mg	=	=	–	–	=
Eletriptan 40 mg	=	=	=	=	=
Eletriptan 80 mg	+	+	+	=	=
Naratriptan 2.5 mg	=	=	=	–	+
Rizatriptan 5 mg	=	=	=	=	=
Rizatriptan 10 mg	=	+	+	+	=
Sumatriptan 25 mg	=	=	=	–	=
Sumatriptan 50 mg	=	=	=	=	=
Sumatriptan 100 mg	=	=	=	=	=
Zolmitriptan 2.5 mg	=	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=	=

+ indicates significantly superior to sumatriptan 100 mg
– indicates significantly inferior to sumatriptan 100 mg
= indicates equivalent to sumatriptan 100 mg

Alternatives which dominate the reference product (and equivalents)

Table 1 shows that the reference product and its 5 equivalents are dominated by 3 alternatives – almotriptan 12.5 mg, eletriptan 80 mg and rizatriptan 10 mg. Thus, neither the reference product and its equivalents nor the 2 products which they dominate are eligible for inclusion in the subset of preferred triptans. Regardless of how the treatment attributes are prioritised for a given patient, there will always be a superior alternative (based on statistically significant differences).

Alternatives which neither dominate nor are dominated by the reference product (and equivalents)

Naratriptan 2.5 mg is not dominated by sumatriptan 100 mg as it has superior performance on tolerability, nor does it dominate, as its performance on consistency is inferior. Naratriptan, however, is dominated by almotriptan 12.5 mg, so cannot be considered a member of the nondominated (preferred) subset.

Fig. 1 shows the complete dominance hierarchy based on the statistically significant results from the meta-analysis. Although the comparisons are with sumatriptan 100 mg rather than direct comparisons among the other products, it is clear from the meta-analytic confidence intervals provided in the source papers that among the 3 products which dominate sumatriptan 100 mg, none is dominant over another. These 3 products, therefore, almotriptan 12.5 mg, eletriptan 80 mg and rizatriptan 10 mg, are not dominated by any other, and each dominates the remaining 9 triptan/dose alternatives. Taken together, they provide statistically significant superiority to the reference product (sumatriptan 100 mg) on all 5 treatment attributes.

Discussion

Although we take a new approach to the analysis and interpretation of the results from Ferrari et al.'s meta-analysis, studies which depend on previously published data are subject to the limitations imposed by those data. For example, the authors of the meta-analysis included only oral triptans – it is possible, for example, that the nasal spray or parenteral formulations might occupy a higher place in the dominance hierarchy – and among oral triptans, frovatriptan was excluded from the analysis (although this exclusion is unlikely to have affected the conclusions of our analysis). One product can be said to dominate another, therefore, relative to the other products included in the analysis, rather than dominating absolutely all triptan formulations.

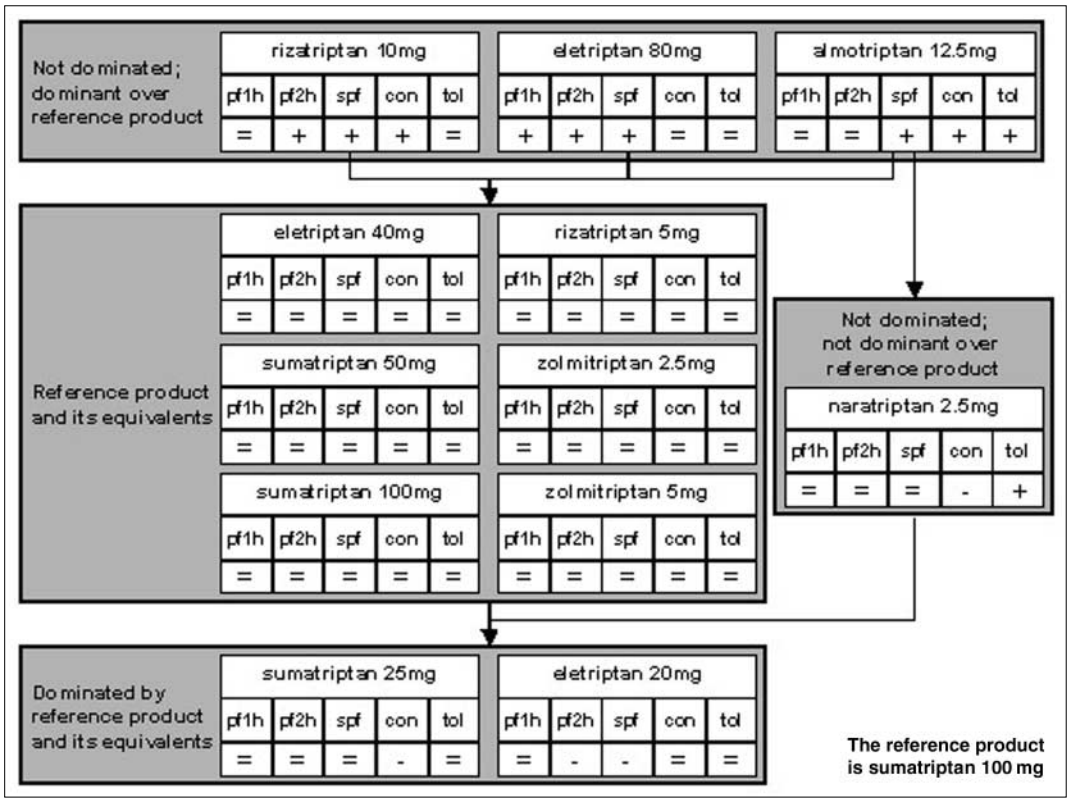

Fig. 1 The dominance hierarchy

Furthermore, our analysis is limited to the treatment attributes included in the meta-analysis; it is possible that the inclusion of additional attributes would lead to a different subset of preferred products. For example, an attribute such as "comfort level" may play a part in prescribing and formulary decisions, favouring older products, and the inclusion of a measure of "value" might also change the subset of preferred triptans.

Despite these limitations, Ferrari et al.'s meta-analysis is the most comprehensive evaluation of the triptans yet published, and application of a dominance criterion to the statistically significant differences found therein led to 3 alternatives being identified as the subset of the nondominated triptans. However, one of these, eletriptan 80 mg, is not approved for use as first-line treatment of acute migraine in either Europe [7] or the United States [8]. Indeed, an 80-mg dose is proscribed by the US labelling: "An 80-mg dose, although also effective, was associated with an increased incidence of adverse events. Therefore, the maximum recommended single dose (of eletriptan) is 40 mg." [8]. Furthermore, the authors of the meta-analysis themselves considered eletriptan 80 mg to be inferior to the reference product with respect to tolerability [5], even though it did not meet their criterion for statistical significance. The "preferred triptans", therefore, comprise the other 2 nondominated alternatives, almotriptan 12.5 mg and rizatriptan 10 mg.

This present analysis confirms and extends the findings from the TRIPSTAR project, in which evaluations of the relative importance of treatment attributes of the oral triptans, collected in surveys in a variety of settings, were combined with meta-analysis outputs in a multiattribute decision model to provide overall evaluations of the triptans, in terms of their similarity to a hypothetical "ideal triptan". In this project, the same 3 triptans, almotriptan, eletriptan and rizatriptan, emerged as the preferred subset, irrespective of whether the attribute importance weights were obtained from neurologists [9], primary care physicians [10] or migraineurs [11, 12]. Similarly, almotriptan, eletriptan and rizatriptan were more similar (than sumatriptan, naratriptan or zolmitriptan) to a hypothetical "ideal triptan", when compared using >10 000 sets of computer-generated importance weights which reflected the entire range of values for relative attribute importance [13].

This new approach to the analysis and interpretation of the results from Ferrari et al.'s meta-analysis [5] indicates that recently introduced triptans can provide superior clinical benefit, and hence, merit inclusion in a physician's therapeutic armamentarium and on clinical formularies.

Acknowledgement This study was supported by a grant from Pharmacia Corporation.

References

1. World Health Organization (2003) The global burden of disease. Epidemiology and burden of disease. World Health Organization, Geneva
2. Lipton RB, Stewart WF (1993) Migraine in the United States: a review of epidemiology and health care use. Neurology 43[6Suppl 3]:S6–S10
3. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML (1999) Burden of migraine in the United States: disability and economic costs. Arch Intern Med 159(8):813–818
4. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine – current understanding and treatment. N Engl J Med 346:257–270
5. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ (2001) Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 358:1668–1675
6. Yoon KP, Hwang C-L (1995) Multiple attribute decision making: an introduction. Sage, Thousand Oaks, pp 38-40
7. British National Formulary, edition 46. http://www.bnf.org/bnf/bnf/current/noframes/106531.htm?q=%22eletriptan%22, accessed March 2004
8. US Product Information for Relpax. http://www.pfizer.com/download/uspi_relpax.pdf, accessed March 2004
9. Dodick DW, Cutrer FM, Ferrari MD, Goadsby PJ, Lipton RB, McCrory DC, Williams P (2002) Prioritization of treatment attributes in selecting an oral triptan: a survey of US neurologists. Headache 42:392
10. Cutrer FM, Goadsby PJ, Ferrari MD, Lipton RB, Dodick DW, McCrory D (2004) Priorities for triptan treatment attributes and the implications for selecting an oral triptan for acute migraine: a study of US primary care physicians (the TRIPSTAR project) Clin Ther 26:1533–1545
11. Lipton RB, Liberman J, Goadsby PJ, Ferrari MD, Dodick DW, Cutrer FM, McCrory D (2002) An assessment of the priorities of US migraineurs with respect to prespecified triptan treatment attributes. Headache 42:394-395
12. Lipton RB, Liberman J, Cutrer FM, Goadsby PJ, Ferrari MD, Dodick DW, McCrory D, Williams P (2004) Treatment preferences and the selection of acute migraine medications: results from a population-based survey. J Headache Pain 5:123–130
13. Ferrari MD, Goadsby PJ, Lipton RB, Dodick DW, Cutrer FM, McCrory D, Williams P (2004) The use of multiattribute decision models in evaluating triptan treatment options in migraine. J Neurol (*in press*)
14. Roon KI, Lipton RB, Goadsby PJ, Ferrari MD (2001) Efficacy of six oral triptans at one-hour post dose: a meta-analysis. Cephalalgia 21:405