Nonadherence to Imatinib Treatment in Patients with Gastrointestinal Stromal Tumors: The ADAGIO Study

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Abstract. *Aim: To determine imatinib nonadherence rates in patients with gastrointestinal tumors (GIST) over 90 days. Patients and Methods: A prospective 90-day observational, open-label, multicenter study was carried out of 28 evaluable GIST patients on imatinib. Nonadherence behavior was measured using a 4-item patient interview. Clinicians, patients, and collaterals rated perceived patient adherence on a 0-100 VAS scale. Results: Nonadherence rates in the 4 weeks prior to baseline and follow-up were 29% (95% CI=26-32) and 24% (95% CI=21-27, p>0.05). Mean VAS ratings of perceived adherence ranged from 95.2±10.2 to 97.3±4.8 (p>0.05 for time and source of rating). Correlations between perceptions of and actual adherence behavior were negative. Conclusion: In this first study on imatinib nonadherence in GIST patients, rates were similar to those observed in patients with chronic myeloid leukemia, higher than clinically expected and exceeding meta-analytic estimates for cancer. Nonadherence rates were consistent across the 90-day period. Nonadherence behavior should be assessed by clinicians.*

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Imatinib mesylate (imatinib) blocks the adenosine triphosphate binding site of the breakpoint cluster region gene and the V-abl Abelson murine leukemia viral oncogene (*BCR-ABL*) tyrosine kinase, and is the first-line chemotherapy management for advanced gastro-intestinal stromal tumors (GIST) (1-7). However, as the management of GIST is long-term if not lifelong, continuous and adequate imatinib dosing is essential to achieve therapeutic outcomes. Patient adherence, *i.e.*, the extent to which a person's behavior corresponds with the agreed upon recommendations of a healthcare provider (8), is therefore critical. The ADAGIO study (Adherence Assessment with Glivec: Indicators and Outcomes) aimed to examine prospectively over a 90-day period, in the real-practice setting, the prevalence of imatinib nonadherence in patients with chronic myeloid leukemia (CML) or GIST on imatinib treatment for at least 30 days (9). We recently reported nonadherence rates of 36.1% and 32.7% (90 days later) among 169 CML patients in the ADAGIO study. In contrast, these patients as well as their physicians and close family members or friends (hereafter referred to as collaterals) rated patient adherence between 94.1 and 97.1 on a 0-100 visual analog scale (VAS), suggesting that adherence perceptions are discordant with actual adherence behavior.

The ADAGIO study also included 28 evaluable patients with GIST. The limited sample size of patients with this rare disease precludes advanced statistical analysis, however we describe here adherence problems observed in this subsample.

Table I. *Correlations of physician, patient, and collateral perceptions of adherent and non-adherent behaviors.*

		Baseline		Follow-up	*P*-value[a]
VAS (mean±SD)	Physician	97.1±4.6		95.2±10.2	>0.05
	Patient	96.6±6.4		95.4±9.2	>0.05
	Collateral	97.3±4.8		96.8±5.8	>0.05
BAAS (95% CI)	All patients	29%		24%	>0.05
	Primary tumor	36%		33%	>0.05
	Relapse	24%		19%	>0.05
	P-value[b]	>0.05		>0.05	
VAS-BAAS Correlation		Baseline r	*P*-value[a]	Follow-up r	*P*-value[a]
	Physician	–0.388	0.042	–0.328	>0.05
	Patient	–0.603	0.001	–0.775	<0.001
	Collateral	–0.563	0.045	–0.924	<0.001
		Baseline	*P*-value[c]	Follow-up	*P*-value[c]
Months on imatinib (mean±SD)	Adherent	19±16	>0.05	22±16	0.009
	Nonadherent	10±14		6±7	

VAS: Visual Analog Scale; BAAS: Basel Assessment of Adherence Scale. [a]*P*-value for comparisons across; [b]*P*-value for comparisons down; [c]*P*-value for comparisons between adherent and nonadherent patients at respective baseline and follow-up.

Patients and Methods

This being a Short Paper, we refer to Noens *et al*. (9) for a detailed description of study design and methodology. Summarized, consenting patients age 14 or older, diagnosed with GIST, and who had been on imatinib for at least 30 days (to permit assessment of adherence in the four weeks prior to enrollment) were observed for a period of 90 days in a prospective multicenter pharmacoepidemiologic observational study. At both baseline and follow-up, physicians used the Basel Assessment of Adherence Scale with immunosuppressive medication, adapted to imatinib (BAAS) (1), a 4-question clinical interview guide about imatinib-related medication behaviors in the preceding 4 weeks ("not having taken your medication sometimes"; "skipped several consecutive doses"; "sometimes taken your medication with more than 2 hours' time difference from the prescribed dosing time"; and "reduced the prescribed amount"). A positive answer to any question constitutes nonadherence. Patients, physicians, and collaterals rated patient adherence on a 10 cm VAS converted to a 0 to 100 score.

Results

A total of 28 GIST patients contributed by 20 physician-investigators in Belgium completed the study with evaluable data, *i.e.*, meeting inclusion criteria, having baseline and follow-up BAAS adherence data, and at least one physician and one patient VAS rating. The mean (±SD) age was 61.6±12.6 years. Two-thirds of the sample were male (67.9%) and all but one patient (92.9%) was Caucasian. One-third of patients (32.2%) had post-secondary education. About half (46.4%) were either retired or on sick leave. The mean time since GIST diagnosis was 3.4±2.4 years. The majority of patients had relapsed disease (60.7%). Most patients (23 or 82.1%) had undergone surgery prior to initiation of imatinib treatment, mainly complete (20 patients) *versus* partial resection (3 patients). Patients had been treated with imatinib for 17.2±15.6 months (median=13.5).

Table I presents VAS ratings of adherence perception and BAAS-determined rates of nonadherence at baseline and follow-up, as well as the correlation coefficients between the various VAS adherence ratings and the BAAS nonadherence assessment at both time points. Summarized, per the BAAS nonadherence rates were 29% and 24% at baseline and follow-up respectively ($p>0.05$). Mean VAS ratings of perceived adherence ranged from 95.2±10.2 to 97.3±4.8 and were not statistically significant from baseline to follow-up across categories of respondents. Correlations between adherence perceptions and actual adherence behavior were negative. While consistent from baseline to follow-up for physician VAS ratings, these negative correlations increased for patients and collaterals (both $p<0.001$). Adherent patients tended to have been on imatinib longer than nonadherent patients.

Per the BAAS, 5 patients adherent at baseline had become nonadherent at follow-up, while for another 5 patients the opposite was observed. Fourteen patients remained adherent from baseline to follow-up. One patient nonadherent at baseline was still so 90 days later (data missing for 3 patients).

Discussion

A retrospective analysis of claims data for 374 patients with CML and 91 patients with GIST found 12-month mean and median persistence of 69.4% and 79.7% across all patients; unfortunately, no disease-specific rates were reported (11). To our knowledge, the 90-day GIST data reported here are the first

prospective data to underscore the problem of patient nonadherence to imatinib treatment among GIST patients. They confirm that nonadherence is a significant problem in this population. Subject to validation in future large-sample studies, there may be a trend towards greater nonadherence among those patients with primary disease compared to those in relapse, and those patients with a longer *versus* shorter imatinib treatment history. In parallel to observations in the CML population, adherence VAS ratings by patients, physicians, and collaterals were consistently above 95 on a 0-100 scale. Not surprisingly, the correlations between these adherence perceptions and actual adherence behavior (as measured by the BAAS) were mainly weak to modest. Surprising, however, was the consistent inverse relationship: high VAS adherence ratings were associated with lower adherence behaviors, and *vice versa*. This is of significant clinical concern, as patients, physicians, and collaterals may overestimate adherence, be inclined to ignore the problem, and potentially compromise treatment outcomes.

Even in this limited sample of GIST patients, imatinib nonadherence rates were similar to those in CML patients, higher than clinically expected, and exceeding meta-analytic estimates for cancer (12). Given that GIST is a rare disease (our sample of 28 patients included most of the estimated 34 cases in Belgium at the time), international studies with larger sample sizes and multiple methods of adherence assessment are needed to assess the impact of nonadherence on treatment outcomes. These studies should also evaluate the determinants of both non-adherence and adherence, differentiating between patient- and physician-related variables (9).

In the interim, however, clinicians should assess for nonadherence routinely to counter incorrect perceptions, determine actual nonadherent behavior, and promote adherence in their GIST patients. Despite the high efficacy of imatinib in the management of GIST and the high likelihood of positive treatment outcomes, clinicians should not assume that this will increase patient adherence.

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Conflicts of Interest

All Authors completed the ICMJE Uniform Disclosure Form. K. Muermans and M.-A. van Lierde are employees of Novartis. I. Abraham and K. MacDonald are employees of Matrix45. By company policy, employees are prohibited from owning equity in client organizations (except through mutual funds or other independently administered collective investment instruments) or contracting independently with client organizations. Matrix45 provides similar services to those described in this article to other biopharmaceutical companies on a non-exclusivity basis.

References

1 Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B and Demetri GD: Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med *344*: 1052-1056, 2001.

2 van Oosterom AT, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, Martens M, Webb A, Sciot R, Van Glabbeke M, Silberman S and Nielsen O, for the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group: Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet *358*: 1421-1423, 2001.

3 Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD and Joensuu H: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med *347*: 472-480, 2002.

4 Scaife CL, Hunt KK, Patel SR, Benjamin RS, Burgess MA, Chen LL, Trent J, Raymond AK, Cormier JN, Pisters PW, Pollock RE and Feig BW: Is there a role for surgery in patients with 'unresectable' cKIT+ gastrointestinal stromal tumors treated with imatinib mesylate? Am J Surg *186*: 665-669, 2003.

5 Nowain A, Bhakta H, Pais S, Kanel G and Verma S: Gastrointestinal stromal tumors: clinical profile, pathogenesis, treatment strategies and prognosis. J Gastroenterol Hepatol *20*: 818-824, 2005.

6 Connolly EM, Gaffney E and Reynolds JV: Gastrointestinal stromal tumours. Br J Surg *90*: 1178-1186, 2003.

7 Dirnhofer S and Leyvraz S: Current standards and progress in understanding and treatment of GIST. Swiss Med Wkly *139*: 90-102, 2009.

8 Sabaté E: Adherence to long-term therapies: evidence for action. Geneva, World Health Organization, 2003.

9 Noens L, van Lierde M-A, De Bock R, Verhoef G, Zachee P, Berneman Z, Martiat P, Mineur P, Van Eygen K, MacDonald K, De Geest S, Albrecht T and Abraham I: Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood *113*: 5401-5411, 2009.

10 Cleemput I, Dobbels F and De Geest S: Measuring patient-reported outcomes in solid organ transplant recipients: an overview of instruments developed to date. Pharmacoeconomics *25*: 269-286, 2007.

11 Halpern R, Barghout V, Mody-Patel N and Williams D: Relationship between compliance, costs, hospitalizations for CML and GIST patients using imatinib mesylate [abstract]. J Clin Oncol *26*: 5S, Abstract 6598, 2008.

12 DiMatteo MR: Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care *42*: 200-209, 2007.

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