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Articolo originale

Original article

Raltegravir use prospectively assessed in a major HIV outpatient clinic in Italy: sample population, virological-immunological activity, and tolerability profile

Valutazione prospettica di raltegravir in un centro italiano di riferimento per la gestione dell'infezione da HIV. Attività virologica-immunologica e profilo di tollerabilità

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INTRODUCTION

Raltegravir as the first available antiretroviral agent belonging to the class of HIV integrase inhibitors, has been introduced and prospectively monitorized since 2010 in our HIV outpatient centre, where over 1,200 patients are currently monitored by a dedicated team including staff physicians and hospital pharmacists [1-7]. The aim of our report is to perform an *interim* assessment of the background, the efficacy and tolerability profile, and the clinical-laboratory monitoring of all experienced patients treated with a combination antiretroviral therapy (cART) including raltegravir, taken for at least 12 months.

PATIENTS AND METHODS

In all, 109 patients (77 males and 32 females; 104 Caucasians and 5 Afro-Americans), started a raltegravir-containing cART when aged 27-73 (mean 44.8±19.2) years, with a history of HIV infection lasting 6-25 (mean 13.4±9.7) years. For this *interim* analysis, all these subjects were monitored for at least 12 months.

Our hospital pharmacy informatized dispensary system and our clinical charts were prospectively filled with data of all patients who received raltegravir. Raltegravir was dispensed according to the international and Italian guidelines of antiretroviral therapy and all manufacturers' recommendations (at the standard dosage of 400 mg twice daily) [8, 9].

For this *interim* analysis, experienced patients who have been receiving a raltegravir-containing cART for at least 12 consecutive months (mean 17.2±10.3, range 12-47 months), were selected. Clinical and electronic charts were prospectively completed in order to record all demographic figures, medical history and laboratory data, information regarding comorbidities, previous and concurrent medications, and to record all visits at our outpatient centre including clinical and laboratory data, and compliance assessment (carried out on the ground of monthly drug accountability, and patients' self-reported written records, double-checked

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at every access together with our hospital pharmacists). Student *t* test and Mantel-Haenszel chi-square test were used for statistical analysis where appropriate, with significance limits posed at $p<.05$.

RESULTS

In the vast majority of cases (93 out of 109 patients: 85.3%), multiple (range: 3 to 16) prior cART therapeutic changes mainly due to failures and/or toxicity, prompted the introduction of raltegravir in salvage, advanced therapeutic lines. 72 of these 109 patients (66.1%) had even developed a concurrent triple-class resistance to nucleos(t)ide reverse trascriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and the majority of protease inhibitors. At the time of raltegravir introduction, the most frequent companion antiretroviral agents were: darunavir/ritonavir (75 cases), maraviroc (47 subjects), and etravirine (38 cases). These last drugs and all other antiretroviral compounds were carefully selected according to previous and current genotypic/phenotypic *in vitro* resistance assays, previous toxicities and intolerances, and underlying disorders and comorbidities, in order to ensure a maximally optimized background to raltegravir adjunct. The majority of our patients (62 out of 109: 56.9%) received a four-drug regimen including raltegravir, a protease inhibitor boosted with ritonavir (mainly darunavir-ritomavir), maraviroc, and etravirine. At the time of the therapeutic switch, and during the subsequent follow-up period of at least 12 months, limited changes to the novel salvage cART regimens became necessary. In particular, the discontinuation of one or more nucleos(t)ide reverse transcriptase inhibitors, that of non-nucleoside reverse transcriptase inhibitors, and that of protease inhibitors, which proved not sufficiently sensitive at genotypic/phenotypic virological assays, or had a poorer tolerability when compared with the novel cART regimens, or did not add anything significant in terms of efficacy, potency, and safety to the remaining components of the last selected cART, was systematically conducted, thus improving cART simplification, and also containing toxicity and costs of unnecessary drugs.

The patients' adherence to raltegravir proved very elevated (from 90% to 100% of prescribed dosages throughout the 12-month study period), together with that of the concurrent cART regimens (90-100%), based on hospital pharmacists' monthly interview, patients' written records, and computerized drug accountability records.

The switch to an optimized cART based on raltegravir favourably affected clinical and laboratory markers of HIV disease progression, and those of the majority of comorbidities, except for two patients who failed their raltegravir-containing combination due to a low adherence period experienced during periodic hemodyalisis in one case, and a prolonged hospitalization period at a rehabilitation facility in another patient (as documented by the specific raltegravir mutations retrieved when sequencing the gp41 HIV protein).

When considering laboratory surrogate markers of HIV disease progression, HIV viraemia (which proved positive in all patients switching to raltegravir), became undetectable (as expressed by plasma HIV-RNA levels below 20 copies/mL) in a short time, ranging from 8 to 16 weeks (mean 6.8±2.5 weeks), since raltegravir introduction. No significant difference was detected when adjusting these data according to the different antiretroviral compounds associated to raltegravir at the time of therapeutic switch, while the 35 patients with a higher viral load (*i.e.*, above 10^5 HIV-RNA copies/mL) took significantly more time compared with the 74 patients with a viraemia above 10^3 copies/mL to reach undetectable levels; $p<.0001$). When assessing the extent and time of immune recovery, an increase of the absolute CD4+ T-lymphocyte count was observed in all the 109 patients switched to a raltegravir-containing cART, as evaluated on the ground of a mean 26.2±15.1% (range 16.9%-178.2%) maximum increase of CD4+ cell count *versus* baseline levels, paralleled by an improvement of mean absolute CD4+ lymphocyte count of 148.7±112.4 cells/μL (the range of peak increase of CD4+ count varied from 69 to 445 cells/μL). The subgroup of 47 patients taking maraviroc plus raltegravir showed a tendency towards an increased mean and peak T-lymphocyte count, as well as a more rapid achievement of the peak of CD4+ lymphocyte count recovery, although these figures did not reach a statistical significance compared with other patient subgroups (due to the proportionally small patient samples).

The most common concurrent disease of our patients were: AIDS (46 patients), liver cirrhosis (31 cases), AIDS-related or other malignancies (23 cases), and major cardio- or cerebro-vascu-

lar events (18 cases). A chronic HCV and HBV hepatitis were of concern in 48 and 23 patients, respectively.
Only three episodes of AIDS-defining conditions became apparent during raltegravir-based cART; chemotherapy and/or radiotherapy cycles were performed as scheduled in all patients suffering from cancer; chronic hepatitis B and C progressed to liver cirrhosis and/or hepatocarcinoma in only 2 and 6 patients, respectively; otherwise, a first or repeated treatment with pegylated interferon-ribavirin became feasible in 25 patients out of 48 with chronic HCV infection.
In only 17 cases on the whole of the evaluable 109 (15.6%), a change of companion drugs was deemed necessary during the 12-month follow-up, including: the introduction of darunavir/ritonavir instead of other protease inhibitors in 7 cases, and the adjunct of maraviroc (6 patients) and etravirine (4 cases), to replace tipranavir/ritonavir (5 cases) enfuvirtide (two subjects), or lamivudine/emtricitabine with or without another nucleos(t)ide reverse transcriptase inhibitor (10 cases).
Despite the already compromised clinical situation at the time of raltegravir introduction, only a minority of subjects experienced mild-transient clinical and/or laboratory untoward events possibly attributable to raltegravir (including gastrointestinal disorders, fatigue, cough, dizziness, insomnia and a self-limited cutaneous rash), although their relationship with the study drug was difficult to establish due to multiple comorbidities and polypharmacy typical of our heavily pre-treated patients, and the predominantly subjective report of most of these complaints. During raltegravir-containing cART treatment, neither relevant respiratory tract infections, nor autoimmune disorders nor novel malignancies were diagnosed in our cohort, despite a special attention was focused on these complications (mentioned as possible untoward events in raltegravir-treated patients). As a whole, raltegravir suspension and/or interruption were not needed in any patient during the entire observation period (12 months or more), save the two patients whose virus became raltegravir-resistant. On the other hand, abnormal liver function testing were observed in 57 patients of 109 (52.3%), all occurring in subjects with underlying chronic hepato-biliary disorders, and with laboratory values always proving ameliorated, when compared with the period immediately preceding the introduction of raltegravir. Unexpected increases in serum triglyceride and lipase levels were never registered, and the complete serum lipid profile (including at least total cholesterol, HDL- and LDL-cholesterol, and triglycerides), showed a consistent and significant improvement after the introduction of raltegravir, compared with baseline levels. In fact, mean serum cholesterol levels dropped from 224.2±34.9 mg/dL to 182.3±17.2 ($p<.001$), mean serum HDL-cholesterol values rose from 38.9±12.3 to 45.6±14.8 mg/dL ($p<.03$), serum LDL cholesterol levels decreased from 168.9±42.1 to 136.9±23.1 mg/dL ($p<.001$), and serum triglyceride levels dropped from 188.2±41.1 to 144.3±26.8 mg/dL ($p<.001$).

DISCUSSION

Raltegravir is the first licensed HIV integrase inhibitor, effective on both antiretroviral-naïve and -experienced patients when associated with an optimized cART, which demonstrated an excellent efficacy profile on surrogate markers of HIV disease progression (with a particularly rapid and enhanced immune recovery), a satisfactory tolerability profile also in patients with underlying comorbidities, proportionally limited drug-drug interactions, and a sufficiently consistent pharmacokinetic-pharmacodynamic profile, which also includes a favourable penetration into relevant HIV sanctuaries, like the central nervous system and the genital tract [1-7].
All these characteristics, together with the lack of cross-resistance with all other anti-HIV compounds belonging to other classes, and the good patient's convenience, make raltegravir a cornerstone of cART, especially for experienced patients with multiple failures and a broad spectrum of HIV resistance mutations or multiple intolerances or contraindications to other antiretroviral drugs and combinations. As mentioned, after randomized clinical trials against efavirenz-containing cART, raltegravir has been also approved for first-line therapy in naïve patients (with nucleos(t)ide-sparing regimens reserved for patients with limited therapeutic options) [1-3, 5, 6].
Our preliminary experience with raltegravir, even after considering the numerous limits due to the proportionally reduced patient sample coming from a single centre, the proportionally short period of prospective observation, the extremely frequent patients' salvage or advanced stage on the ground of HIV antiviral resistance

profile (occurring in many cases after a prolonged history of HIV disease and multiple previous treatment failures or changes), an already progressed and complicated HIV disease, and the related and unrelated comorbidities, underlines the excellent efficacy and safety profile of raltegravir also in the common daily practice. By exploiting a novel mechanism of action, in absence of cross-resistance with all other antiretrovirals, raltegravir has been associated with an effective, optimized background cART, in order to strengthen and simplify antiretroviral therapy of patients as far as possible, as currently recommended [2, 3, 7-9].

When analyzing efficacy figures, also data from double-blind phase III randomized trials of raltegravir associated with an optimized background given to patients who experienced cART failure with triple-class resistance (combined data from BENCHMRK 1 and 2 trials), represent a situation very similar to our prospective experience conducted in daily practice [1].

In the quoted registration trials [1], among the 462 patients posed on raltegravir plus an optimized background and examined at week 48, an undetectable viral load (HIV-RNA <50 copies/mL) was detected in 62.7% of evaluable cases (with factors predictive of failure including a baseline viraemia >100,000 HIV-RNA copies/mL, and a background therapy not including at least one active agent) [1]. From a virological point of view, our viremic patients posed on raltegravir achieved a sustained undetectability level (set at HIV-RNA levels <20 copies/mL) of 97% at 12 months of follow-up. The two virological failures associated with raltegravir mutations were attributable to a proven, reduced patients' compliance to the entire cART regimen, and were expected when using a first-generation integrase inhibitor which requires a fully supportive antiretroviral background to protect it from its proportionally low genetic barrier (which is shared with elvitegravir, but not completely with dolutegravir and further integrase inhibitors in the pipeline, which are exposed to a reduced activity only after multiple resistance mutations) [10, 11]. In an Italian National surveillance study performed on 101 triple-class experienced patients receiving a raltgravir-based cART, a 25.7% rate of virological failure was shown, in absence of possibly predictive baseline factors (including gender, age, route of HIV transmission, baseline HIV-RNA levels, CD4+ lymphocyte count, hepatitis B or C co-infection, previous genotypic resistance profile, type and number of concomitant anti-HIV drugs, and health-related quality of life measures), thus suggesting that a close patient-caregiver alliance and a careful monitoring of adherence levels and eventual unfavourable drug-drug interactions, should deserve maximum consideration to enhance an effective, sustained response to raltegravir-containing cART [11].

A very satisfactory immunological response has been also observed in our single-centre cohort, as expressed my a mean peak increase of absolute CD4+ T-lymphocyte count of 148.7±112.4 cells/μL, which compared very well with data stemming from early registration trials of raltegravir [1]. Dealing with the mechanisms of action of the study drug, the significant increase of CD4+ lymphocyte count obtained in patients under raltegravir may result from a specific drug action, as well as a better capability or the drug to reach all body compartments with suitable concentrations [2-4, 14].

The tendency to obtain a further increase of mean and peak CD4+ T-lymphocyte count in our subgroup of patients receiving also maraviroc, failed to reach statistical significance due to the proportionally reduced patient samples in our experience. A recent meta-analysis from the literature did not show a further, significant increase of CD4+ cell count when maraviroc was added to an optimized cART based on raltegravir [7].

Other notable experiences reported by the literature have been conducted with raltegravir in settings comparable with ours (*i.e.*, daily clinical practice). In particular, the Aquitaine cohort carried out a first observational study of raltegravir plus optimized background in 51 highly pretreated patients under clinical routine conditions [12]. At week 24, 78% of evaluable patients experienced virological success, and the median CD4+ increase was 57 cells/μL, with a reduced immune response independently associated with a lower viral load decline; raltegravir-related mutations emerged in 9 out of 11 failing patients [12]. A second experience from the Aquitaine cohort assessed 170 patients with multidrug-resistant HIV infection and HIV replication already suppressed (HIV-RNA levels <400 copies/mL), switching from enfuvirtide-based regimens to a raltegravir-based optimized cART: the therapeutic change maintained a sustained antiviral efficacy (HIV-RNA <50 copies/mL), together with a stable CD4+ T-lym-

phocyte count, and proved better tolerated, although 18.2% of patients experienced an increase in serum transaminase levels, mostly attributed to tipranavir-ritonavir co-administration [13]. Another recent French study performed in 482 raltegravir-treated patients evaluable after 12 months in a real-life setting like ours, reported an elevated rate and varieties of co-morbidities, a variable adherence rate, but confirmed excellent efficacy and tolerability figures , which were comparable to that observed in randomized registration trials [1, 14].

A favourable tolerability profile has been demonstrated for raltegravir since earlier registration studies, with headache and gastrointestinal complaints representing the most common reported adverse events, while mild neuropsychiatric disorders have been been infrequently recorded (all of them usually reported on subjective basis), together with extremely rare cases of rhabdomyolisis and hypersensitivity reactions, while the serum lipid profile was fully respected by raltegravir, especially when compared with regimens containing older protease inhibitors, and efavirenz too so that raltegravir should represent a preferred option for patients with a preexisting risk of cardiovascular diseases, altered serum lipid levels, metabolic syndrome, or changes in body fat composition (*i.e.*, the lipodystrophy syndrome) [1, 5, 6, 15]. Also in our case mix, a statistically significant improvement in serum lipid levels occurred, regardless of the composition of the previous cART regimens. In our case series no clinical and laboratory evidences of autoimmune disorders were identified, as also reported in a recent 12-month observational study regarding exposure to raltegravir-containing cART regimens [16].

On the whole, in our prospective observational experience, grade 2-4 adverse events attributable to raltegravir were neither directly observed, nor reported in the self-recorded file of possible untoward events filled every month by our patients at the time of repeated prescription, and double-checked by our hospital pharmacists and physicians in charge, leading to a discontinuation rate due to toxicity-intolerance virtually equal to zero.

On the other hand, the discontinuation of some companion drugs at the time of raltegravir introduction and during the 12-month follow-up (especially nucleos(t)ide reverse transcriptase inhibitors, some selected protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and enfuvirtide), acted favourably on the tolerability of the raltegravir-based regimens, especially when checking our patients for cardiovascular risk factors, serum lipid profile (serum total, LDL-, and HDL-cholesterol, serum triglycerides), serum glucose and Hb1c, renal function parameters, and subjective untoward events like gastrointestinal disorders as a whole, lipodistrophy syndrome, central nervous system complaints, and cutaneous manifestations.

Coming to patients with a concurrent, chronic HCV and/or HBV co-infection, a recent nationwide Italian patient revision allowed to show that raltegravir therapy plus an optimized background slightly increases the incidence and severity of clinical and laboratory liver-related abnormalities of HIV-patients co-infected with either HCV or HBV, without increased risks of treatment interruption [17]. A very similar situation has been disclosed in our single-centre cohort. On the reverse, the virological and immunological response to salvage regimens based on raltegravir and an optimized background in these difficult-to-treat patient, is not affected negatively by HCV and HBV co-infection, according to the same Italian survey [17]. Data from our prospective observational study confirm this tendency, underlining that the immune system recovery granted by the switch to a raltegravir-based optimized cART allows the start or a rechallenge of pegylated interferon-ribavirin therapy in an appreciable rate of HCV-infected patients (31.3% in our experience).

In fact, the favourable immunological recovery granted by raltegravir-containing cART regimens could prompt the introduction of raltegravir in patients with a discordant virological-immunological response to previous cART lines, especially when an underlying chronic hepatitis or liver cirrhosis are present.

Further pilot experiences demonstrated the efficacy and safety of novel antiretroviral combinations sparing both nuclos(t)ide reverse transcriptase inhibitors and protease inhibitors, especially in three-class experienced HIV-infected patients: the association of maraviroc, raltegravir and etravirine seems particularly promising in this setting [18]. The excellent efficacy and tolerability profile makes raltegravir a preferred target for both intensification and simplification cART regimens: in this last case, raltegravir introduction might save expected, unnecessary toxicities, and also crude costs due

to nucleos(t)ide reverse transcriptase inhibitors and boosted protease inhibitors [3].
Finally, also from a pharmacoeconomic point of view, recent evaluations performed with Markov cohort models, showed remarkable advantages in terms of efficacy, when introducing raltegravir plus an optimized antiretroviral background in individuals with limited cART options, regardless of the choice of active companion drugs, and also in antiretroviral-naïve subjects [19]. Encouraging pharmacoeconomic data are expected from raltegravir, when assessed on the ground of its adherence levels, according to a recent Italian assessment [20].
In conclusion, in our cohort of over one hundred heavily experienced HIV-infected patients with frequent comorbidities were prospectively monitored for at least 12 months while on raltegravir plus an optimized cART, the rate of virological and immunological success and the incidence and severity of untoward events proved at least similar or even better when compared to the most relevant registration studies of raltegravir in experienced patients, so that we can consider raltegravir as an effective and safe choice for these difficult-to-treat subsets of HIV-infected patients, also in routine, real-life clinical conditions [1].
A progressively extended prescription in naïve patients and early cART lines will allow the therapeutic potential of raltegravir to be exploited [2, 7-9].

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Keywords: HIV infection, antiretroviral therapy, raltegravir.

SUMMARY

Raltegravir, as the first HIV integrase inhibitor, has been used and prospectively monitored since 2010 in our HIV outpatient centre, where over 1,200 patients are monitored. The aim of our report is to perform an *interim* assessment of the background, the safety profile and the clinical-laboratory monitoring of all patients treated with a combination antiretroviral therapy (cART) including raltegravir, for at least 12 months. In all, 109 pretreated patients started a raltegravir-containing cART when aged 44.8±19.2 years, with a history of HIV infection lasting 13.4±9.7 years. All subjects were monitored for at least 12 months (mean 17.2±10.3 months). In the vast majority of cases (93 of 109: 85.3%), multiple (3-16) prior cART changes prompted raltegravir introduction in advanced-salvage lines: 72 of 109 (66.1%) patients had even developed a concurrent triple-class resistance to anti-HIV compounds. The most frequent companion antiretroviral agents were: darunavir/ritonavir (75 cases), maraviroc (47 subjects), and etravirine (38 cases). The most common underlying conditions were: AIDS (46 patients), liver cirrhosis (31 cases), AIDS-related or other malignancies (23 cases), and major cardio-cerebro-vascular events (18 cases). A chronic HCV and HBV hepatitis were of concern in 48 and 23 patients, respectively. The adjunct of raltegravir favourably affected all clinical-laboratory markers of HIV disease progression, and those of the broad spectrum of comorbidities, except for two patients who failed the raltegravir-containing cART due to insufficient adherence. Despite the already compromised clinical situation, a minority of subjects experienced mild-transient clinical-laboratory untoward events possibly attributable to raltegravir, such that no patients discontinued raltegravir during the observation period. Only three AIDS-defining conditions became apparent during raltegravir-based cART; chemotherapy and/or radiotherapy cycles were performed as scheduled in patients suffering from cancer; chronic hepatitis B and C progressed to liver cirrhosis and/or hepatocarcinoma in only 2 and 6 patients. Otherwise, treatment with pegylated interferon-ribavirin became feasible in 25 patients of 48 with chronic HCV. During raltegravir-containing cART, neither autoimmune disorders nor novel malignancies were diagnosed. Only mild-transient gastrointestinal disorders, fatigue, dizziness, insomnia and cutaneous rash were reported, although their relationship with the study drug was difficult to assess due to multiple comorbidities and polypharmacy. Abnormal liver function testings were observed in 57 patients (52.3%), all suffering from concurrent hepato-biliary disorders. Significant increases in serum lipids and/or lipase levels *versus* baseline values were never registered: serum lipid levels significantly improved after raltegravir introduction.
Our experience with raltegravir underlines its excellent efficacy and safety profile, which exploits a novel mechanism of action, and displays no cross-resistance with any other antiretroviral. A progressively extended prescription in naïve patients and early cART lines will allow the therapeutic potential of raltegravir to be exploited.

RIASSUNTO

Raltegravir, primo inibitore dell'integrasi di HIV disponibile, è stato impiegato e monitorizzato in via prospettica fin dal 2010 presso il nostro Centro ambulatoriale, dove seguiamo oltre 1.200 pazienti con infezione da HIV. Scopo del nostro studio è riportare una valutazione ad interim *del* background*, e del monitoraggio clinico-laboratoristico e della sicurezza di tutti i pazienti* experienced*, trattati con una terapia antiretrovirale di combinazione (cART) comprendente raltegravir, per almeno 12 mesi. Centonove pazienti pretrattati hanno intrapreso una cART contenente raltegravir quando avevano un'età media di 44,8±19,2 anni, e una storia di infezione da HIV della durata 13,4±9,7 anni. Tutti i soggetti sono stati seguiti per almeno 12 mesi (media 17,2±10,3 mesi).*

Nella grande maggioranza dei casi (93 su 109: 85,3%), molteplici (3-16) cambiamenti di cART hanno preceduto l'introduzione di regimi di salvataggio avanzato comprendenti raltegravir: ben 72 di questi 109 pazienti (66,1%) aveva sviluppato una resistenza concomitante a tre classi di antiretrovirali. Gli agenti anti-HIV più frequentemente somministrati in associazione erano: darunavir/ritonavir (75 casi), maraviroc (47), ed etravirina (38). Le patologie concomitanti più frequenti erano: AIDS conclamata (46 pazienti), cirrosi epatica (31), neoplasie correlate o non ad AIDS (23), ed eventi cardio- e cerebro-vascolari maggiori (18 casi). Un'epatite cronica da HCV e HBV si associava rispettivamente in 28 e 23 pazienti. La cART contenente raltegravir agiva favorevolmente su tutti i marcatori clinico-laboratoristici di progressione dell'infezione da HIV, e su quelli dell'ampio spettro di comorbilità presenti, salvo che in due pazienti, in cui si registrava un fallimento della cART contenente raltegravir, dovuto ad insufficiente aderenza. Nonostante la situazione di base compromessa, solo una minoranza di soggetti lamentava lievi-transitori eventi avversi clinici e di laboratorio potenzialmente attribuibili a raltegravir, cosicché nessun paziente doveva interrompere la terapia durante il periodo di osservazione. In corso di cART contenente raltegravir, si palesavano soltanto tre eventi clinici definenti l'AIDS, mentre cicli di chemioterapia e/o radioterapia venivano praticati come previsto in pazienti affetti da patologie tumorali; un'epatite B o C progrediva verso la cirrosi epatica e/o un epatocarcinoma in soli 2 e 6 pazienti; mentre un trattamento con interferone pegilato-ribavirina diveniva effettuabile in 25 pazienti su 48 affetti da epatite cronica da HCV. In corso di cART basata su raltegravir, non si evidenziavano disordini autoimmuni né nuove patologie tumorali. Venivamo riportati soltanto lievi-transitori disturbi gastrointestinali, faticabilità, vertigini, insonnia e rash cutanei, ma la loro correlazione con il farmaco in studio risultava di difficile valutazione per le multiple comorbilità e la polifarmacologia. Alterazioni dei test di funzionalità epatica si osservavano in 57 pazienti (52,3%), tutti affetti da concomitanti patologie epato-biliari. Non si registravano mai incrementi significativi dei lipidi sierici e/o dei livelli di lipasi rispetto ai valori al basale: anzi, la lipidemia plasmatica migliorava nel suo complesso dopo l'introduzione di raltegravir.

La nostra esperienza con raltegravir sottolinea l'eccellente profilo di efficacia e tollerabilità, che sfrutta un innovativo meccanismo d'azione, in assenza di resistenza crociata con altri antiretrovirali. Un progressivo incremento delle prescrizioni anche in pazienti naïve *e fin dalle prime linee terapeutiche, permetterà di sfruttare il potenziale terapeutico di raltegravir.*

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