Biomedicines as Adverse Event Inducers

Biomedicines are new agents with old roots. Products of biological origin, such as vaccines, blood and serum components, human proteins, hormones, and immunoglobulins, are used from long time in human therapy.

After the discovery of a technique for producing monoclonal antibodies in 1975, and the first commercialization of muromonab in 1986 for the control of solid organ graft rejection, their expansion has been exponentially growing, leading to the development of new drug classes for the treatment of tumors, autoimmune diseases, and inflammatory diseases.

Their extraordinary efficacy, the parallel expansion of genetic engineering, and the increased knowledge on the physiopathology of the immune system soon stimulated the identification and production of other biologically active molecules, including fusion proteins, growth factors, hematopoietic stimulating factors, and other cytokines for therapeutic use such as enhancers, inhibitors, and antagonists of basic cell functions and of immune effector mechanisms.

The first cytokine-based therapy reached the market in 1986 with IFN-α2b and IFN-α2a. A recent business intelligence report retrieved 504 mAbs in clinical and market stages up to February 2013. By the end of 2011, about 270 new cytokine therapies, including cytokines, mimic-cytokines, cytokine inhibitors, and/or cytokine receptors were developed and investigated. Annual sales for cytokines, including IFN α/β, ESAs, and Hemopoietic Growth Factors, exceeded $1 billion in the same year. Annual sales of 30 monoclonal antibodies approved in US generated $ 44 billion in 2011. Adalimumab (Humira®), one of the top selling drugs worldwide in 2012, is expected to reach $13.7 billion in 2013.

Over a quarter of century of experience on efficacy and safety of most relevant new biomedicines has been so far accumulated.

Soon after the first clinical controlled experiences, it was clear that biomedicines could raise a number of adverse effects, sometimes impressive and life threatening. Muromonab showed extraordinary beneficial effects in the control of acute graft rejection, but they were associated to a heavy safety profile, including cardio-respiratory disorders, neuro-psychiatric events, serious infections, increase of malignancy rates, fatal anaphylaxis, and violent systemic reactions such as

CRS, even during the first infusion. It was also evident that the increasing commercialization of new biomedicines and the expansion of indications of these products would have increased insurgence and incidence of new typologies of adverse events. Meanwhile, the growing availability of long-term clinical data and of more biomedicines with similar therapeutic indications, gradually offered the possibility of more solid and comprehensive evaluations on their safety, as single therapeutic agents or as drug classes sharing structural and/or functional properties.

On this basis, having initially examined the safety frameworks of the most relevant products of the area, some comparative analyses and common peculiarities in the generation of adverse events of some drug classes can be attempted.

In principle, AEs pathogenesis of biomedicines can be attributed to their mechanism of action and/or to their immunogenicity, i.e., to the consequences of targeting specific cell structures such as receptors or ligands, or to the specific structure of biodedicines, mostly consisting of glycoproteins containing animal (rodent) and/or human sequences. The first group of AEs can be considered consequent or associated to the pharmacological activity of the biomedicines, while the reactions caused by their immunogenicity are dependent mostly on the typical macromolecular, proteic structure of the agent, which acts as a strong foreign antigen promptly recognized by the recipient's immune system.

While AEs of the former group are frequently, but not always, linked to the therapeutic effect of the biomedicine, the latter reactions may not, and can not interfere with clinical effects by reducing drug availability. Therefore, during biomedicines' development it resulted urgent and more feasible to reduce their immunogenicity by progressive humanization of the molecules, up to fully human protein sequencing and glycosylation, than trying to dissect the efficiency from adverse reactivity, the "bonus" from "malus" activity at clinical level. Humanization procedures sharply reduced immunogenicity, although they were neither able to abolish AEs, nor to avoid their most severe and life threatening expressions [1, 2]. In fact, even fully humanization could not produce "stealth" molecules, since their structure can be still recognized as an allogenic "foreignness," yet able to induce sensitization of the recipient, and provoke hypersensitivity reactions of all types and severity.

However, surprising cases of tolerability were also experienced. For example, one patient previously showing a severe anaphylactic reaction to the chimeric murine basiliximab could receive the humanized daclizumab directed to the same IL-2R-α chain, without any adverse effects. Notably, the patient had a positive skin test to basiliximab and to horse and rabbit polyclonal anti-thymocyte antibody preparation, but not to daclizumab after prick and intradermal testing [3].

An alternative approach to reduce AEs among mAbs ($\simeq 147$ kD) was the truncation of the Fc fragment, when the therapeutic effect was not critically linked to the expression of CDC and/or ADCC. In this case the shortage of the half-life of the remaining Fab portion was compensated by coupling the remaining Fab fragment with PEG, leading to products with reasonable durability and a lower AEs potentiality. For example, certolizumab is a pegylated recombinant

humanized Fab fragment (91 kD) composed of a single light and heavy chain derived from a murine IgG2a antibody, directed against soluble and transmembrane TNFα. The overall safety profile resulted more selective than other members of the same drug class. The absence of the Fc fragment avoided CDC and ADCC-dependent reactions. However, the incidence of infections and in particular of granulomatous infections, including new cases or reactivation of TB, were not reduced, thus indicating their strict relation to the Fab-mediated portion of the molecule and very likely to the expressed mechanism of action. Abciximab is a smaller fragment (47.6 Da) consisting in a disulfide-linked dimer of an Fd heavy chain fragment and an intact light chain. It is directed against the CD41 integrin and inhibits platelet aggregation. The safety profile consisted in hemorrhagic complications, strictly related to its mechanism of action, but also to its immunogenicity, which caused ITCP.

Pegylation has been used also for preparing therapeutic formulations of interferons (peg-IFNα-2a, and 2b), erythropoetins (peginesatide, peg-epoetinβ), of hemopoietic growth factors (pegfilgrastim), and mAbs (cetuximab) leading to improvement of their half-life and to mitigation of immunogenicity.

By contrast, in the case of fusion proteins, usually the addition of a human Fc fragment was necessary to express CDC/ADCC effector functions and increase their half-life, which inevitably carried some AEs enhancement as well.

Efforts to imbalance the risk/benefit ratio in favor of the latter were also attempted by increasing the affinity of the agent for its target. However, this was not always the case: motavizumab, for example, which was developed by affinity maturation from palivizumab, did not show a better efficiency, yet higher rates of AEs, SAEs, and death. Attempts to improve edrecolomab efficacy by increasing affinity up to 100 fold produced modest clinical results, but serious toxicities. By contrast, nimotuzumab—showing a lower affinity for EGFR, one log lower than cetuximab and 2 logs lower than panitumumab—apparently expressed a better safety profile in this drug class, without showing striking differences in terms of relative efficiency. In this case, the lower affinity seemed to better discriminate EGFR overexpressing neoplastic cells from normal epithelial cells, thus achieving a better risk/benefit balance. Notably, in these cases, as in others, the skin seemed to be a particularly sensitive target in evidencing, and discriminating among different safety profiles.

When immune-mediated effector functions were not needed in the mAb molecule, the IgG2 isotype was chosen, being an irrelevant inducer of CDC and ADCC activity, thus avoiding the related AEs events. This is the case of panitumumab, tositumomab, and daclizumab. Alternatively, the IgG4 backbone virtually not binding complement was preferred, such as for natalizumab, and gemtuzumab, or a hybrid IgG2/IgG4 combination as in eculizumab to take advantage of both properties.

Glycosylation was not immediately considered a crucial characteristic of biomedicines, but it became clear that the quality and quantity of glycosylation interfered with CDC and ADCC activity, as well as with immunogenicity, and therefore with the induction of AEs. For example daclizumab and the DAC HYP

analog have the same amino-acid sequence but a different glycosylation pattern affecting the binding of the latter molecule to the Fc receptors, resulting in decreased CDC and ADCC activity, expected to improve safety without altering efficiency.

Anomalous glycosylation patterns may provoke unexpected, unwanted immune reactions. In the case of cetuximab, its expansion in the murine Sp 2/0 cell line transferred galactose-α-1,3-galactose on the heavy chain of the Fab fragment, which at first infusion induced a severe IgE-mediated anaphylactic reaction, due to pre-existing antibodies in cetuximab recipients [4].

Glycosylation variability has also been of concern in the production of some biosimilar biomedicines, such as erythropoetins. In fact such variability, among others, can influence immunogenicity and has caused problems for the approval of some growth hormone biosimilars [5]. With this respect, the preparation of syalo-carbomylated and non-glycosylated erythropoietin recent formulations may help in better understanding their role in immunogenicity, and in AEs induction.

Taken together, it became evident that "biological" molecules fulfilled expectations more in terms of efficacy than in being "innocuous" or "invisible" to the immune system. Therefore, AEs will continue to be part of biomedicines' therapeutic scenery, although with milder characteristics when compared to chemotherapeutics and to other immunosuppressive drugs, but also with some additional peculiarities mostly related to their glycoproteic structure.

On this basis, in line with the general classification for all adverse drug-related events (see Chap. 2), AEs to biomedicines can be identified as:

(A) *AEs related to the mechanism of action*: They may derive from a direct and specific action (direct toxicity, induction of apoptosis), or as a consequence of the drug-target binding causing secondary toxicities (cytokine release, tumor lysis syndrome).

(B) *AEs related to the immunogenicity of the molecule*: They may occur as a consequence of hypersensitivity reactions triggered by the biomedicine recognition as a foreign complex of antigens, or by cross-link antigenicity with pre-existing antibodies or sensitized T cells.

However, some peculiarities need to be underlined. Predictability of DRAEs is mainly assigned to Type A reactions, while unpredictable immune-related Type B reactions are usually restricted to predisposed individuals (see Table 2.1). The overall frequency of ADEs was estimated to be over 80 % for Type A, and 10–20 % for Type B.

In the case of biomedicines, predictability is not so clear-cut between the two ADEs groups. One possible reason is the existence of multiple mechanisms, only partially known, involved in the pharmacological action of these agents. Moreover, being biomedicines proteic structures with a relatively high molecular weight they have high immunogenic potential; Type B reactions are expected to be more relevant than for small chemical therapeutic molecules. The different degree of "humanization" easily proved the possibility of reducing such immunogenic potential and the consequent capacity of inducing AEs, although leaving large margins of variability.

Therefore, a higher level of unpredictability in Type A and a higher frequency and variability in immune-related Type B than non-biological drugs are to be expected. The latter type of reactions in the case of biomedicines seems to be involved mainly in early events and in the reduction of pharmacological efficiency.

Finally, due to their relatively high immunogenic potential, ADEs induced by biomedicines (BAEs, Table 2.4) must be envisaged from a larger population of individuals than those usually identified as "predisposed," "genetically predisposed," or "atopic" subjects. However, these concepts better fit with specific hapten-directed immune events, more than with the more general reactivity to large multi-antigenic proteic structures.

In conclusion, ADEs in the treatment with biomedicines are an obligatory companion, which must be known, interpreted, prevented, and managed. Interestingly, the unwanted companion in some instances appears so strictly related to drug's efficiency to become a prognostic factor of clinical response, such as rash for cetuximab.

Two further approaches to reduce immune reactivity to biomedicines relate to procedures for *deimmunization* and *desensitization*. The former, in line with the mentioned more coarse techniques of mAb splitting and elimination of Fc fragment, is a new technology that allows to locate and selectively remove T cell epitopes responsible for the expression of immunogenicity within the variable region sequences of mAb, fusion proteins, or from any other proteic structure. Importantly, this technique influences the immunogenicity of the structural area involved in the mechanism of action of these biomedicines [6].

Desensitization is a known procedure widely used to mitigate allergic reactions to insect venoms and pollens. In this case the potential offending agent is administered in a stepwise, highly controlled regimen. Such procedure has been adopted, for example, to mitigate infusion reactions after rituximab, infliximab, cetuximab, and trastuzumab among others [7].

Both approaches deserve more attention from clinicians and biomedicines' manufacturers to mitigate and prevent the insurgence of undesired events.

Provided that the AEs expression variability is elevated among biomedicines and that experience is still limited with the most advanced formulations, it may be nonetheless useful for practical purposes to depict:

(1) The *general safety profile* of most relevant and frequent adverse events
(2) The *drug class safety profile*, at least for those categories represented by more than two therapeutic formulations.

In attempting to depict a *general safety profile* it is useful to group the analyzed biomedicines according to their common target, as reported in Table 58.1, which may help in better individuating shared AEs more strictly related to a similar mechanism of action. These agents can be also distinguished for having inhibitory effects (Class 1–10) or stimulatory effects (Class 11). In particular, among the inhibitory classes some are more strictly related to the targeted molecule, while other are more broadly grouped according to the targeted cell type/s. Typical target-specific groups are TNF inhibitors (Class1), anti-VEGF agents (Class 4), and anti-EGFR (Class 5). By contrast, Class 2 is characterized by the targeted

Table 58.1 Classes of biomedicines

Class	Target	Main expression Inhibitory effect	Biomedicines
1	TNFα	Soluble and on T, M, Mθ, NK	Adalimumab
			Certolizumab
			Golimumab
			Infliximab
	TNFR	T, M, Mθ, NK	Etanercept
2	IL-1R	Ubiquitous	Anakinra
	CD25 (in IL-2R)	aT, aB, THY, MYpr, ODC	Basiliximab
			Daclizumab
	α-4β1, α-4β7(integrin)	T, B, M, Mθ, Bas, E	Natalizumab
	CD52	T,B, M/Mθ, NK(50 %)	Alemtuzumab
	IL6R (CD126/130)	Soluble and on T, B, G, F, Mθ	Tocilizumab
	CD11a (LFA-1)	T, B, Mθ, N	Efalimumab
	IL-2R	T, B, NK, M	Aldesleukin
			Denileukin-DT
	CD33	MY, M, ERpr	Gemtuzumab
	CD20	pre-B, B	Ibritumomab
			Ofatumumab
			Rituximab
			Tositumomab
	BLyS (TNF family)	Soluble	Belimumab
	CD80/CD86	T, DC	Abatacept
			Belatacept
	CD2	T	Alefacept
	CD3	T	Muronomab
	CD30 (TNF family)	Th2	Brentuximab
	CTLA-4 (CD152)	aT	Ipilimumab
3	IL-1β	Soluble	Canakinumab
	IL-1α, IL-1β	Soluble	Rilonacept
	IL-12/IL-23	Soluble	Ustekinumab
4	VEGF	Ep, E, R, F, M, Mθ, NEU	Aflibercept
			Bevacizumab
			Ranibizumab

Table 58.1 (continued)

Class	Target	Main expression	Biomedicines
		Inhibitory effect	
5	EGFR	Epithelia	Cetuximab
			Nimotuzumab
			Panitumumab
	EpCAM	Epithelia	Catumaxomab
			Edrecolomab
	HER-2 (CD340)	Epithelia	Pertuzumab
			Trastuzumab
	EpGFR (epidermal)	Epithelia, Keratinocytes	Palifermin
			Becaplermin
6	RANKL	OB, OC, BMSC, other	Denosumab
7	IFNAR	Epithelia, Virus infected cells	rHuIFN-α, -β
	IFNGR		rHuIFN-γ
8	RSV	Respiratory Syncytial Virus	Palivizumab
9	CD41	Thrombocytes	Abciximab
10	C5	Soluble	Eculizumab
	IgE	Soluble	Omalizumab
		Stimulatory effect	
11	IL-11R	Blood cell precursors	Oprelvekin
	TPOR	Thrombocytes	Romiplostim
	EPOR	ERpr	rHuEPO-α, -β
			Darbepoetin–α
	GFR	G, M	Filgrastim
			Sargramostim
	SCR	BMSC, PBPC	Ancestim

aN activated neutrophils; aT, aB activated lymphocytes; Bas basophils; BMSC bone marrow stem cells; DC dendritic cells; E eosinophils; E/Ep endothelia/precursors; ERpr erythroid precursors; F fibroblasts; G granulocytes; M monocytes; Mpr myeloid precursors; MY/MYpr myeloid cell lineage/precursors; Mθ macrophages; N neutrophils; NEU neurons; NK natural killer cells; OB, OC osteoblasts, osteoclasts; PBPC peripheral blood presursor cells; R renal cells; T,B lymphocytes; Th2 T-helper cells; THY Thymocytes. See also list of acronyms.

cells, mostly represented by mAbs directed to a variety of molecules expressed on WBC, either widely shared or specifically restricted to a cell type (T, B) or even to a subgroup of them (Th, aT). Clearly, whenever inhibitory effects are directed against downregulators of the immune response (CD8+T cells, Treg), overstimulation, and autoimmune reactions can be expected as outwardly paradoxical

Table 58.2 Classes of biomedicines and their safety profiles

Class	Inhibitory effect			Safety profile	
	Target	Biomedicine	BBW	Main additional group features	
1	TNFα	Adalimumab	SI, TB, M	OI, TB	
		Certolizumab	SI, TB, M	H/A	
		Golimumab	SI, TB, M	M: L/LK, HSTCL, TCL,NMSC, Solid tumors	
		Infliximab	SI, TB, M	HBV, DD (MS, GBS, PNP, etc.): exacerbation and new	
	TNFR	Etanercept	SI, TB, M	HF: LLS; CP	
2	IL-1R	Anakinra	–	SI, H/A, IR, M, NP, ISR (TNF inhibitors increase infections)	
	CD25 (in IL-2R)	Basiliximab	–	I, IR, H/A, HYP, PY	
		Daclizumab	–	CT, H/A, HYP, HYG, PY, GI,WH, Edema, Tachycardia, Bleeding Thrombosis	
	α-4β1, α-4β7(integrin)	Natalizumab	PML	H/A, HT, SI, IR, IRIS, WBC and nucleated RBC increase	
	CD52	Alemtuzumab	CT, SI, IR	A,OI (CMV), IR	
	IL6R (CD126/130)	Tocilizumab	SI	A, CT, DD, GIP, HT, ILD, IR, M, MAS, NP, OI,TCP, TB, WH Dyslipidemia	
	CD11a (LFA-1)	Efalizumab	PML, SI	OI (CMV),DD (GBS, PNP), IHA, M, NF, ITCP, DW	
	IL-2R	Aldesleukin	CLS, DI, CT	PY, TCP, HT, NPD, AKF, Chemotaxis impairment	
		Denileukin-DT	CLS, IR, V	HT, Hypoalbuminemia, Visual and color acuity disorders	
	CD33	Gemtuzumab	H/A, IR, HT	Severe pulmonary events during IR, TLS	
	CD20	Ibritumomab	MCR, IR, CP	MDS/AML, FT, ST (SJS, exfoliative dermatitis, etc.)	
		Ofatumumab	–	IR, CP (NP), SI (OI), PML, HBV, IO	
		Rituximab	IR, TLS, MCR, PML	SI, HBV, CT, GIP, RT, CP, Hypo-Ig	
		Tositumomab	H/A, CP, RE	M (MDS/AML, solid tumors), Hypothyroidism, FT	
	BLyS (TNF family)	Belimumab-fh-IV	–	SI, H/A, Depression, Increased mortality	
	CD80/CD86	Abatacept	–	H/A, SI,TB, M, IR, (TNF inhibitors increase infections; COPD increase respiratory AEs)	
		Belatacept	SI, M(PTLD)	PML, OI (CMV), TB, PVN, Solid tumors, NMSC, HYP, Dyslipidemia	
	CD2	Alefacept	–	SI, M (NMSC, HL, NHL), H/A, HT, LP	
	CD3	Muromonab			
	CD30°	Brentuximab -ch-IV	PML	PNP (mostly sensory), IR, NP, TLS, PML, SJS,	
	CTLA-4 (CD152)	Ipilimumab	IMAE	IMAE: hepatitis, endocrinopathies, SJS, TEN, Enterocolitis, GBS, PNP	

Table 58.2 (continued)

Class	Inhibitory effect		BBW	Safety profile
	Target	Biomedicine		Main additional group features
3	IL-1β	Canakinumab	–	SI (URTI, some OI), H/A, ISR, (TNF inhibitors increase infections)
	IL-1α, IL-1β	Rilonacept	–	SI (URTI, bacterial meningitis), H/A, ISR, Dyslipidemia (TNF inhibitors increase infections)
	IL-12/IL-23	Ustekinumab	–	SI (Mycobacteria. BGC, Salmonella), M (solid tumors), H/A, RPLS
4	VEGF	Bevacizumab	HD, GIP, WH	Hemorrhage, non-GIP, ATE, HYP, RPLS, Proteinuria, IR, ovarian failure
		Aflibercept (zaltrap)	HD, GIP, WH	Hemorrhage, non-GIP, ATE, HYP, RPLS, Proteinuria, IR,NP, Diarrhea
		Aflibercept (eylea)	–	SI (endophthalmitis), Retinal detachment, IOP, ATE
		Ranibizumab	–	SI (endophthalmitis), Retinal detachment, IOP, ATE, D (DME)
5	EGFR	Cetuximab	IR, CT	Cardiopulmonry arrest, PT (ILD), ST (acneiform rash), Hypomagnesemia
		Nimotuzumab	–	IR, HYP, ST (mild), PY, Hypomagnesemia
	EpCAM	Catumaxomab	–	CRS, SIRS, GI disorders, HYP, LP, SI, Rash
		Edrecolomab		GI disorders (diarrhea), H/A
	HER-2 (CD340)	Pertuzumab	FT	LVEF dysfunction, IR, H/A
		Trastuzumab	IR, CT, PT, FT	LVEF dysfunction, ILD, NP, Anemia, SI, RT, TE, Diarrhea
	EpGFR (epidermal)	Palifermin	–	M (epithhelial), Rash, Tongue/taste altered, Dysesthesia, Lipase/amylase increase
		Becaplermin	M	M (local and distant; increased mortality)
6	RANKL	Denosumab	–	Hypocalcemia/phosphatemia, ONJ, FT
7	IFNAR	rHuIFN-α, rHuIFN-β	–	NPD, HT, H/A, CHF, LKP, AID (ITCP, AIH, THY), Seizures
	IFN-alfacon-1	synthetic IFN-α	D	D:(in NPD, AID, SI, CVD). FT, PT, HT, RF, H/A, OD, AID, PNP, Colitis, Pancreatitis
	IFNGR	rHuIFN-γ	–	CT, CRS/FLS, HT, NPD, ISR
8	RSV	Palivizumab	–	H/A, PY, TCP, ISR, Rash
9	CD41	Abciximab		TCP, Bradycardia, H/A, ARDS, Hemorrhage
10	C5	Eculizumab	SI	SI (meningo, strepto, haemophilus), IR. URTI, Tachycardia
	IgE	Omalizumab	–	H/A, TCP, ISR

Table 58.2 (continued)

Class	Inhibitory effect			Safety profile	
	Target	Biomedicine	BBW	Main additional group features	
11	IL-11R	Oprelvekin	H/A	CLS, Edema (facial, pulmonary), Papilledema, Anemia (dilutional), CT, RF	
	TPOR	Romiplostim	–	M (MDS/AML progression), TE, TCP, BMRF, Erythromelalgia	
	EPOR	rHuEPO-α, rHuEPO-β	M, CT	D (in CKD), M (progress/recurr; solid/lymphoid), H/A, HYP, Seizures, PRCA, Stroke	
		Darbepoetin-α	M, CT, TE, D	D (in CKD), M (progress/recurr; solid/lymphoid), H/A, HYP, Seizures, PRCA, Stroke	
	GFR	Filgrastim/ pegfilgrastim	–	Splenic rupture, Bone pain, ARDS, H/A, Sickle cell crisis, M (MDS/AML), ISR	
		Sargramostim	–	CLS, Edema, CT, RF	
	SCR	Ancestim	–	H/A, M (SCLC, MCL, MM), Leukocytosis, ISR (distant recall)	

A anaphylaxis; AID autoimmune disorders; AIH autoimmune hepatitis; AKF acute kidney failure; ANAs anti-nuclear antibodies, all types; ARDS acute respiratory distress syndrome; ATE artero-thrombotic event; BMRF bone marrow reticulin formation; CHF congestive heart failure; CKD chronic kidney disease; CLS capillaty leak syndrome; CMV cytomegalovirus; COPD chronic obstructive pulmonary disease; CP cytopenia; CRS/FLS cytokine release syndrome/ flu-like syndrome; CT cardiotoxicity; CVD cerebrovascular disorders (stroke, etc.); exacerbation and new; D death (increased mortality); DD demyelinating disorders; DME diabetic macular edema; DW disease worsening (in treatment); FT fetal toxicity; GBS Guillain Barré syndrome; GI gastrointestinal disorders; GIP gastrointestinal perforation; H, H/A hypersensivity, and including anaphylaxis; HBVr hepatitis B virus reactivation; HD hemorrhagic disorders; HF heart failure, all type; HL Hodgkin lymphoma; HSTCL hepato-splenic Tcell lymphoma; HT hematotoxicity/bone marrow toxicity; HYG hyperglycemia; HYP hypertension; IHA immune hemolytic anemia; ILD interstitial lung disease; IMAE immune-mediated adverse events (Tcell activation); IO intestinal obstruction; L/LK lymphoma/ Leukemia; IOP intraocular ocular pressure (increased); IR infusion reaction; IRIS immune restoration inflammatory syndrome; ISR injection site reaction; ITCP immune thrombocytopenia; LKP leukopenia; LLS lupus-like syndrome; LP lymphopenia; LVEF left ventricular ejection fraction; M malignancy; MAS macrophage activating syndrome; MCL mastcell leukemia; MCR muco-cutaneous reaction; MDS/AML myelodisplastic syndrome/acute myeloid leukemia; MM malignant melanoma; MS multiple Sclerosis; NF necrotizing fascitis; NHL non-Hodgkin lymphoma; NMSC non melanoma skin cancer; NP neutropenia; NPD neuro-psychiatric disorders; OD ocular disorders; OI oppertunistic infections, all type; ONJ osteonecrosis of the jaw; PML progressive multifocal leucoenchephalopathy; PNP peripheral Neuropathy (polyneuropathy); PRCA pure red cell aplasia; PSD psychiatric disorders; PT pulmonary toxicity; PTLD post-transplant lymphoproliferative disorder; PRCA pure red cell aplasia; PSD psychiatric disorders; PT pulmonary toxicity; PTLD post-transplant lymphoproliferative disorder; PVN polyoma virus nephropathy; PY pyrexia (relevant); RE radiation exposure; RPLS reversible posterior leukoencephalitis syndrome; RT renal toxicity; SCLC small cell lung cancer; SI serious infections; SIRS systemic inflammatory response syndrome; ST skin toxicity; TB tuberculosis (reactivation and new); TCL T cell lymphoma; TCP thrombocytopenia; TE thromboembolism; TEN toxic epidermal necrolysis; THY thyroiditis (autoimmune); URTI upper respiratory tract infections; WH wound healing retardation
See also list of acronyms

effects. Finally, some agents directed to specific targets act as carriers of toxins (denileukin-diftitox) or radionuclides (ibritumumab-tiuxetan-Yttrium, tositumo-mab-iodine), thus combining therapeutic actions and adverse reactions as well. They have a limited use and cannot be assimilated into a specific drug class.

On this basis, a specific *drug class safety profile* can be attempted, as summarized in the following Table 58.2.

58.1   General Safety Profile

58.1.1 Infusion Reactions and Injection Site Reactions

Possibly the most common and typical early event following biomedicines administrations, infusion reactions, usually occur during the first or second exposure. They are generally well tolerated, manageable, and in part prevented or mitigated by prophylactic therapy, but can be severe and sometimes fatal. Their incidence can be observed well over 50 % of recipients after mAbs administration such as, alemtuzumab, gemtuzumab, or rituximab, and at lower frequency with fully human products, such as panitumumab (about 5 %). This kind of reactions is generally non dose-dependent, and can be partially masked/mitigated by premedication.

Seven biomedicines (alemtuzumab, gemtuzumab, ibritumomab, rituximab, cetuximab, trastuzumab, and denileukin) have a BBW on infusion reactions, indicating their potential severity in their expression. They are not directed to the same targets, but five of them are mainly expressed on leukocytes and two are directed to epithelial surface molecules. Similarly, they do not pertaining to the same structural class and include mAbs, fusion proteins, cytokines, and cytokine receptor analogues. However, 12 additional agents can induce infusion reactions without having a special warning for them. Overall, 13/19 involved biomedicines are directed to cell surface structures expressed by leukocytes (mainly on T cells, B cells, and monocytes), 4 were directed to epithelial cells, and 2 against VEGF molecules (Table 58.1).

Importantly, infusion reactions tend to decrease over time at subsequent administrations. This phenomenon has been attributed to a hypothetical "acquired tolerance", yet to be ascertained.

Infusion reactions have been also attributed to the presence of pre-existing antibodies against murine or human antigens in normal subjects, cross-linking with the respective analogs inserted in the mAb structure. More frequently they appear induced by direct action on immune-related receptors and ligands, inhibited or stimulated by a number of biomedicines, mimicking such events, and even producing impressive systemic reactions such as CRS. TLS, and SIRS (see Chap. 3). The role of glycosylation in modulating these responses has been previously mentioned.

Fusion proteins indicated for intravenous administration appeared to elicit a lower number of reactions, such as belatacept (5–25 %), abatacept (6 %), and denileukin diftitox (8 %) underlining the crucial role of the Fc fragment, which was truncated in these formulations.

Altogether, these events are difficult to distinguish from concurrent classical hypersensitivity Type I (IgE-mediated) and Type II cytotoxic (IgG/IgM- mediated) reactions in response to their immunogenicity.

It must be stressed that the existence of drug-induced allergic responses was already known for low molecular weight conventional drugs, which can trigger

immune reactivity either acting as haptens conjugated to endogenous proteins after administration, or by direct interaction with immune receptors [8], even after non-covalent binding to MHC and TCR molecules [9].

Injection site reactions with biomedicines, anyway injected, are frequent, but usually not worrisome. Etanercept can induce reactions in over 40 % of patients, but have the tendency to decrease with prolonged use, a trend observed also with other biomedicines. Histologically, they showed CD8+ T lymphocyte and eosin-ophil infiltration, with an increased expression of HLA-DR on keratinocytes [10]. Occasional severe ulcerated necrotic reactions were observed with IFN formula-tions, and in particular with IFN-β2b [12]. Noteworthy, most systemic treatments with conventional drugs, especially directed against cancer, are associated with similar reactions during which it is difficult to distinguish hypersensitivity phe-nomena from direct toxicities induced by the various agents often administered in complex combinations. However, reactions caused by biomedicines tend to appear earlier and at the very first administration. For all of them accurate prevention, proper administration, and symptomatic therapy are crucial to significantly miti-gate their effect [10–12].

58.1.2 Infections

Infectious complications are common events during treatment with biomedicines inducing direct or indirect immunosuppression, thus causing a transient secondary immunodeficiency that can be profound and prolonged.

All TNF inhibitors are relevant inducers of infections. They differ both in typology (e.g., TB and other opportunistic infections, mainly Pneuocystis Histo-plasmosis) and frequency (higher with infliximab than with etanercept, etc.), although rarely reaching statistical significance in comparative analyses.

Ten biomedicines have a BBW for serious infections. They can be all included in Type A reactions, and pertain mainly to Classes 1, 2, and 10 (with a BBW warning), and to Classes 3, 4, and 7 (without a BBW). Indeed, in these groups infections are particularly severe. They include fungal, viral, TB reactivation or new onsets, and other opportunistic infections with a trend to be disseminated.

In the case of local (intravitreal) administrations, aflibercept, ranibizumab, and bevacizumab (in off-label administration) cause endophthalmitis, which is infre-quent albeit serious.

From this overall experience some relevant proofs of concept have emerged in relation to the crucial role of distinct receptors and ligands, blocked by biomed-icines, in immune defense from specific infectious agents.

Eculizumab, blocking the C5 factor and the consequent activation of terminal complement cascade, showed its fundamental role in the protection against Neisseria infections, thus mimicking the rare cases of C5 complement congenital deficiency observed in humans.

The reactivation or new insurgence of TB during anti TNF-α therapy indicated the key role of this cytokine pathway in organizing the defense against myco-bacterial infection and in the modulation of inflammatory granuloma formation. Moreover, the experience of various biomedicines available in the anti-TNF drug class revealed the existence of a hierarchy among inhibiting signals expressed by a different incidence and gravity of emerging infections, which were also influenced by the underlying disease under treatment [see also certolizumab, Chap. 14].

The reactivation of viruses, such as HBV, EBV, and JC virus had been observed in a number of clinical conditions during treatment. In particular, cases of HBV reactivation and/or possible new infections were observed with certolizumab, ef-alizumab, etanercept, golimumab, infliximab, muromonab, ofatumumab, ritux-imab, tocilizumab, and ustekinumab. Reactivation of EBV was observed with alemtuzumab, belatacept, brentuximab, canakinumab, daclizumab, and muromo-nab. Finally, the most intriguing JC virus reactivation was detected after belata-cept, efalizumab, natalizumab, rituximab, and tocilizumab. The wider spectrum of pathways intercepted by biomedicines indicated that virus replication and diffusion are under the control of many immune mechanisms, although the TNF pathway appeared particularly important.

JC virus reactivation was particularly concerning because of the rapid induction of PML. In particular, the insurgence after natalizumab treatment clearly indicated the role of integrins, which are involved both in the T cell trafficking and cell adhesion. Moreover, natalizumab mobilizes CD34+ hemopoietic cells—which are considered a reservoir of JCV—thus contributing to virus diffusion to CNS, being such transfer through BBB possibly facilitated by the anti-integrin effect of the monoclonal. These recent data may help in designing more selective biomedicines, with the aim of improving the risk/benefit balance.

The virus activation observed with efalizumab was also instructive. In fact, this mAb was particularly active in inducing viral and mycobacterial infections, including PML and TB infections, indicating the crucial role of another integrin (LFA-1R) in these processes. Efalizumab was withdrawn from market in 2009.

The overall incidence of infections is increased by all immunosuppressive biomedicines, and when particularly effective they cause also opportunistic infections whit a tendency to be disseminated. Comparative data on 8 mAbs, 3 fusion proteins, and one IL-1R antagonist (anakinra) indicated a higher risk of serious infections with certolizumab, infliximab, and tocilizumab; thus indicating possible differences related to the respective mechanisms of action, as repeatedly reported in this volume. In contrast, the risk of TB appeared increased (OR: 4.68, 95 % CI 1.18 to 18.60) for the whole group of examined biomedicines [13].

Importantly, patient's accurate selection, antibiotic prophylaxis, and close monitoring are crucial for their control.

58.1.3 Hematological Events

Hematotoxicity is common among biomedicines and for some of them this event was expected, being strictly related to their mechanism of action. This is the case of abciximab, an anti-GPIIB/IIIa receptor specifically blocking platelet aggregation causing hemorrhage. However, in the case of alemtuzumab, an anti-CD52 protein expressed on virtually all immune cells but not on megakaryocytes and platelets, a less expected diffuse hematotoxicity included severe (up to 50 % of cases in some studies) and fatal cases of TCP, which only in a minority of cases were found to be immune-mediated (ITCP). Similarly, mild to severe unexpected events were also observed after the administration of agents not specifically directed to bone marrow and blood cell components. For example, TCP was observed after efalizumab (anti-integrin), infliximab (anti-TNF), and rituximab (anti-CD20, exclusive of B cells). In the case of efalizumab, an immune-mediated thrombocytopenic activity was detected in some cases.

Among anti TNF-α agents, thrombocytopenia, as well as neutropenia, hyper-coagulability, pancytopenia, and aplastic anemia are uncommon, but can be fatal. Interestingly, it seems that in vitro TNF-α can elicit both stimulatory and inhibitory effects on hemopoietic progenitors, which would indicate that under certain conditions anti-TNF therapy may also induce inhibiting effects on hemopoietic stem cells differentiation [14]. In the case of rituximab, an anti-CD20 transmembrane differentiating agent virtually expressed only on B cells, thrombocytopenia was observed in about 11 % of cases and was serious in over 4 %. Notably, rituximab was effective in restoring platelet levels in ITCP, yet for unexplained reasons, since levels of anti-platelet antibodies remained unchanged in these patients, while the platelet counts increased [see rituximab, Chap. 35]. Hematotoxicity signs are also reported for gemtuzumab (conjugated with the cytotoxic antibiotic ozogamicin), pertuzumab, ofatumumab, tocilizumab, trastuzumab, aldesleukin, denileukin (conjugated with diphteria toxin), and IFNs.

Overall, the pathogenetic mechanisms of a number of drug-related blood disorders remain substantially unknown, yet they are often included into the wide and vague category of "bone-marrow toxicities." Therefore, several aspects of hematotoxicity not directly related to the therapeutic mechanisms of action still need to be investigated, in order to better understand their pathogenesis, and hopefully develop agents in which secondary mechanisms of toxicity could be split off.

Meanwhile, accurate pre-clinical investigation, patient's selection and supportive therapy, also with the powerful bone marrow stimulating factors, are crucial for the control and mitigation of such events.

58.1.4 Anti-Drug Antibody Response

The induction of various types of antibody response is a frequent event with biomedicines for reasons repeatedly mentioned. Anti-drug antibodies may be

developed against mAbs and fusion proteins, either murine (HAMA), chimeric (HACA) or human (HAHA), mainly as IgG, but also as IgM, IgA, and IgE in more limited occasions [15]. Less frequently, these antibodies are neutralizing, and consistently interact with pharmacokinetics of the injected drug [16]. In fact, they impact on safety and efficacy of biomedicines, through altered biodistribution and clearance of the product.

Although mitigated by a number of procedures [2], they remain a major concern, and therefore specific guidelines for their assessment during development of biotechnology-derived therapeutic proteins were issued by some control Agencies [17]. The incidence of such antibodies ranges from about 5 to 65 % according to— yet not strictly dependent on—their level of humanization. The major consequences are immediate adverse reactions and reduction of drug efficiency due to the presence of neutralizing antibodies [16, 18]. However, their presence and role not always appears sufficiently investigated, such as with respect to the Ig subclass role on specific AE outcomes. In some instances, it is surprising that their presence was reported not to interfere with clinical efficiency with respect to observed clearance of the drug in study. Quite rare are specific investigations on IgE presence during Type I hypersensitivity reactions.

58.1.5 Autoimmune Events

Agents interfering with the regulation of the immune system, through immuno-suppressive or immunostimulating actions are expected to imbalance the endogenous immunosurveillance, thus enhancing the possibility for autoreactive cell clones to sneak through. Autoimmune phenomena, such as the production of autoantibodies, exacerbation of pre-existing autoimmune diseases or insurgence of new immune disorders, have all been observed during and after the aministration of a number of biomedicines. Overall, they tend to be expressed more frequently in patients with existing immune dysregulations or overt autoimmune disease. For example, exacerbation and new cases of rheumatic disorders were observed with abatacept (Ps), adalimumab (demyelinating disorders), anakinra (RA), certo-lizumab (RA, CD, Ps), efalizumab (Ps), etanercept (demyelinating disorders), golimumab and infliximab (palmar pustular psoriasis), natalizumab (CD), us-tekinumab (Ps), and rituximab (Ps). Aldesleukin showed a complex multi organ safety profile including new onset and exacerbation of autoimmune disorders. It must be stressed that these complications are quite distinct from rebounding of autoimmune disorders undergoing treatment after therapy interruption or discontinuation.

Among autoimmune conditions particularly evidenced during such treatments there are the lupus-like syndrome (LLS), autoimmune thyroiditis, and autoimmune colitis.

LLS was infrequently observed with natalizumab, rituximab, infliximab, eta-nercept, certolizumab, alemtuzumab, and adalimumab. The syndrome is associated

with the presence of autoantibodies (ANA, dsDNA), but has not been observed in all antibody-positive patients. Interestingly, LLS tended to subside after therapy discontinuation.

Autoimmune thyroiditis was frequently observed after off-label alemtuzumab administration reaching 25 % of treated MS patients. However, thyroid dysfunction is a common event during treatment with IFNs, IL-2, TYK inhibitors, ipilimumab, tositumomab, daclizumab, abatacept, denileukin-diftitox, and with non-biological agents. In particular, primary hypothyroidism is the most common occurring event, but cases of hyperthyroidism and thyrotoxicosis have been also described. The overall incidence ranges from 20 to 50 % of treated cases, but possibly the amount of the drug-induced dysfunction has been underestimated because of the existence of a number of subclinical forms, often confounded by underlying disease symptoms [19].

Autoimmune enterocolitis/colitis and hepatitis have been observed after ipilimumab and tremelimumab (now in Phase III advanced evaluation with unsatisfactory results) administration, both acting as inhibitors of CTLA-4, a member of the Ig superfamily expressed on T cells including Treg lymphocytes. CTLA-4 generates inhibiting signals on T cells and APC cells. Notably, complete knockout of CTLA-4 signals is lethal in animal models and induce massive infiltration of T cells into parenchymal tissues, leading to organ destruction.

Cases of autoimmune hepatitis were also observed after etanercept, infliximab daclizumab, tocilizumab, and after IL-2 (aldesleukin, denileukin) treatment. Noteworthy, fatal cases of autoimmune hepatitis were also observed with IFNs (α, β, and γ).

Some of these disorders are partially reversible after therapy discontinuation. Unfortunately, their prevention is unsatisfactory or not possible. Administration of oral iodine is usually performed before and during treatment for prevention of hypothyroidism. However, cases of hypothyroidism related to the administration of saturated solutions of potassium iodine have also been reported.

58.1.6 Cutaneous Reactions

Skin is a highly sensitive monitor of ADEs, either immune-mediated or not. It has been calculated that cutaneous eruptions are related to drugs in 1–8 % of cases, but these figures appear clearly underestimated when referred to biomedicines. Acute and chronic reactions may involve epithelial, dermal, and vascular skin components with various clinical expressions, from mild to life-threatening syndromes. Generally, mild cutaneous BAEs include rash, maculopapular eruptions, fixed drug eruptions, urticaria, purpura, and vasculitis as the major representative clinical expressions. Severe, life-threatening conditions are mainly represented by Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and a more complex and generalized pathology recently called drug-induced hypersensitivity syndrome (DIHS) or drug reaction with

eosinophilia and systemic symptoms (DRESS), characterized by variable skin eruptions, pyrexia and multi-organ involvement associated to signs of lymphocyte activation (lymphadenopathy, lymphocytosis, atypical circulating lymphocytes) eosinophilia, and to frequent endogenous virus reactivation.

Biomedicines with immunosuppressive activity, mainly targeting T cells (muromonab, efalizumab, alefacept, abatacept), anti-TNF agents (adalimumab, infliximab, etanercept), or consisting in IL-2 formulations and in EGF topical and systemic formulations can promote serious cutaneous events (SJS, exfoliative dermatitis, acneiform dermatitis, palmar-plantar erythrodysesthesia) including the insurgence of cutaneous tumors and other distant epithelial malignancies. Signs of severe skin toxicity have been observed with ibritumomab, bevacizumab, cetuximab, nimotuzumab, panitumumab, and trastuzumab.

It must be noted that the skin microenvironment shows some immune autoregulatory peculiarities, which may explain its exquisite local reactivity to allergens, drugs, and some paradoxical events observed during biomedicines' administration. For example, adalimumab showed to increase the number of Langerhans cells in healing psoriasic plaques, thus suggesting that these specialized cutaneous dendritic cells were somehow involved in an anti-inflammatory process induced by the mAb with favorable consequences for the psoriasic disorder [20].

Estimation of the real incidence and prevalence of cutaneous ADEs are difficult, because of the lack of dedicated studies with observational controlled data collection. Some available estimated rates range from 1.8 to 7 cases per 1,000 hospitalized patients. This type of data collection clearly indicates that milder ADEs not requiring hospitalizations were not considered, and therefore figures are likely underestimated being referred only to most serious events.

Systematic overall estimations of cutaneous BAEs are lacking. A network meta-analysis and Cochrane overview performed in 2011 limited the investigation to 9 biomedicines for TB reactivation, serious infections, and lymphoma indicating higher rates in treated groups, but no data were evaluated at cutaneous level. Other studies limited the safety evaluations to specific drug classes, such as anti-TNF agents, and to serious events. Moreover, some biomedicines used in cutaneous pathologies mimic cutaneous ADEs, or induce exacerbation of pre-existing disease, or add new cutaneous events to pre-existing events, thus increasing difficulties in diagnostic interpretation and etiological assessment.

Recently, a number of cutaneous reactions associated with the use of some biomedicines (mainly, TNF inhibitors) were indicated as mimicking skin diseases, and included: psoriasiform eruptions associated with both anti-TNF agents and with rHuGM-CSF; lichenoid eruptions, vasculitis, LLS, linear IgA eruptions associated to rHuGM-CSF administration; acneiform eruptions mainly associated with anti-EGFR agents (cetuximab, panitumumab, nimotuzumab); interstitial granulomatous dermatitis, alopecia, hirsutism, and other hair disorders [21].

The case of anti-EGFR biomedicines (cetuximab, panitumumab) is instructive, since the epidermis is an ineludible co-target of these mAbs directed to epithelial tumors originating in other organs and tissues. Monoclonals induce acute rash and

acneiform dermatitis distinct from acne vulgaris and resistant, when not worsened, by topical therapy for acne. This ADE is so strictly linked to the mechanism of action of the anti-EGFR agents that eruptions not only correlate with their administration, but they are considered a positive prognostic sign.

Surprisingly, the third anti-EGFR mAb, nimotuzumab, showed a lack of severe skin reactions; rash was practically absent and tolerability was considered excellent also for extra cutaneous AEs (see nimotuzumab, Chap. 28).

Finally, a relevant confounding factor in assessing cutaneous ADEs derives from their clinical evaluation, usually not performed by dermatologists in this kind of safety observations.

58.1.7 Cardiotoxicity

Mild to moderate signs of cardiotoxicity are experienced during therapy with biomedicines, mainly in patients with a pre-existing history of cardiovascular disorders. In fact, macromolecules, such as mAbs and FPs do not have substantial access to ion channels in the myocardium, and therefore they are not expected to affect ion currents or channel selectivity as usually occurring with small molecule drugs. Nonetheless, higher rates and more serious events were observed with adalimumab, aflibercept, bevacizumab, etanercept infliximab, pertuzumab, tocilizumab, trastuzumab, and ustekinumab, inducing a number of CHF, LVEF decrease, myocardial infarction, and other functional disorders. Moreover, because of elevated TNF-α in advanced heart failure, their antagonists were proposed and experienced for therapy with lack of efficacy and increase in mortality.

The case of trastuzumab is instructive, since cardiotoxicity seems related to its mechanism of action inducing HER2 blockade. HER2 is overexpressed in epithelial breast cancer cells, but is crucial in MOMP mitochondrial functioning. In fact, cardiotoxicity seems related to the blocking of downstream HER2 signaling causing membrane permeabilization of myocytes, cytochrome-c release, caspase activation resulting in apoptosis, impaired contractility, and LVEF decrease. Furthermore, trastuzumab inhibits neuregulin1 (NRG1), a protein acting on EGFR, which is essential for heart functioning (see Chap. 38).

It must be noted that some of cardiotoxic effects are reversible, but may also be aggravated by therapeutic associations, such as with anthracyclines [22]. Efforts are being made to separate anti-tumoral from cardiotoxic effects, and to individuate preventive screenings for cardiotoxicity during pre-clinical development [23].

58.1.8 Systemic Syndromes

A number of systemic syndromes mostly related to massive cytokine release and/ or other bioactive cellular components have been described in Chap. 3, and Table 3.1. They include CRS, CLS, TLS, IRIS, SIRS, and MAC expressing a

variety of symptoms, from mild flu-like signs to life-threatening impressive reactions. PML and RPLS are considered localized forms of IRIS and CLS, respectively. Table 3.2 reports biomedicines more frequently capable of their induction. These syndromes remain mostly uncommon/rare and moderate events, and are preventable and manageable, but in a minority of cases they can be deleterious.

A recent and intriguing new phenomenon is related to the induction of immune-related (mediated) adverse events (IrAEs or IMAEs) as a consequence of therapy with biomedicines exerting an enhanced activity of immune aggression, such as after ipilimumab administration. In this case the inhibition of a natural inhibiting signal mediated by CTLA-4, triggers a number of multiorgan inflammatory processes driven by the massive activation oT cells. IrAEs are highly concerning, yet to be fully investigated and understood (see Chap. 25)

58.1.9 Malignancies

A number of biomedicines express immunosuppressive actions, and therefore they are all considered therapies at risk of malignancy, whether or not an effective increase in tumor incidence was observed during controlled studies. The unwanted effect is considered not linked to direct oncogenic properties of these agents, but to a lowering of immunosurveillance on abnormal proliferating cell clones escaping destruction by cytotoxic effector immune mechanisms.

Most of these agents are used in autoimmune and inflammatory diseases, which already have higher rates of malignancies with respect to the background of the healthy population. Therefore, in most cases, data on the ADE-related increased risk of malignancies are controversial. Anti-TNF agents, such as adalimumab, certolizumab, daclizumab, etanercept, golimumab, and infliximab, as well as biomedicines directed against T, B, other leukocytes, and accessory immune cells are reported as potential inducers of malignancies, with variable and controversial frequencies. Anti-TNF agents are considered at higher risk mainly of lymphoma and leukemia, especially in children and adolescents. However, it must be noted that the area of therapeutic intervention consists of populations per se at higher risk of malignancy, such as rheumatic diseases. Skin cancer, and in particular NMSC, is among the most represented epithelial induced neoplasm, followed by a number of other solid tumors. In some instances, peculiar types of neoplasms were apparently increased after treatment with specific biomedicines. For example, the risk for hepatosplenic T cell lymphoma was increased in IBD young patients treated with infliximab. Malignancies were also expected and observed after radiolabeled mAbs (Ibritumomab-tiuxetan-[90]Yttrium; Iodine[131] tositumomab) treatment, including MDS, AML and a number of solid tumors, although rates were not particularly increased in long-term observations. Epoetins iincrease tumor progression and recurrence. EGF, such as becaplermin and palifermin, respectively used for treatment of severe oral mucositis and for diabetic ulcers at

lower extremities, show a consistent stimulation of tumor growth, with increased related mortality, and insurgence mainly of solid tumors in various districts distant from the site of application. Finally, a higher risk for malignancy was theoretically anticipated for ustekinumab, because of potential oncogenic activities of both IL-12 and IL-23 combined with the immunosuppressive effects of this mAb. In fact, epithelial tumors and melanoma in situ were observed, although significantly increased values were confirmed only for NMSC.

Taken together, the risk of malignancy is apparently real in these treatments, but is difficult to estimate in relation to the respective diseased population, while comparison with rates in the normal populations are questionable because of the lack of data on fairly matched groups. An additional confounder consists in the frequent association with immunosuppressive chemotherapy, known to exert further oncogenic effects.

58.1.10   Other AEs Typologies

Constitutional signs and gastrointestinal signs, which represent common reactions to many drugs, rarely show peculiarities during treatments with biomedicines, compared to standard chemotherapy, or other immunosuppressive interventions, which are usually more serious and frequent.

Agents targeting VEFG, such as bevacizumab and aflibercept are particularly aggressive at gastrointestinal level, causing also perforations. Similarly, although to a minor level, cetuximab (anti EGFR), ipilimumab (anti-integrin), and tocilizumab (anti IL-6R) expressed intestinal toxicity and cases of perforation, which mainly are related to underlying pathological conditions (e.g. diverticulitis).

Neuropsychiatric events, as vascular accidents, demyelinating disorders, or infectious complications and cognitive disorders do not show distinctive features or particular associations with specific biomedicines. Neuropathies are also expressed with some frequency during treatment with a number of biomedicines, without showing a peculiar relation with their mechanisms of action or structure. IFNs is associated with an increased trend for psychotic and suicidal disorders. PML and RPLS are specific syndromes observed during treatment with mAbs such as natalizumab, rituximab, brentuximab, ustekinumab, and others [Table 3.2].

At respiratory level, most complications related to infections, which are particularly frequent as nasopharyngitis, URTI, and pneumonia. Interstitial lung disease (ILD) is considered among signs of pulmonary toxicity, and was observed after cetuximab, rituximab, panitumumab, trastuzumab, and etanercept, while COPD was observed after infliximab, rituximab, and etanercept, mainly as exacerbations of previous underlying pathology.

Interestingly, the endocrine system, except for the mentioned autoimmune thyroiditis (see 58.1.5) is not particularly involved. Rare cases of hypophysitis caused by ipilimumab, and more rare cases of diabetes (etanercept) appeared to be rather protected from biomedicines' complications.

58.2   Drug Class Analysis

Having considered individual safety profiles of biomedicines, and most relevant typologies of related AEs, attempts to consider their distribution according to the major drug classes of biomedicines can be instructive.

In Table 58.2 the biomedicines in study are grouped according to the previously described targeted classes. For each product a synthetic safety profile consisting in BBW specifically issued so far, and a number of additional warnings considered more relevant and typical, is reported. Their allocation in the table, allows also the identification of the overall characteristics within each group, as well as the relevant differences in safety profiles among classes and individual agents.

58.2.1 TNF Inhibitors

The essential safety triad expressed by TNF inhibitors includes serious infections, TB reactivation and new, and malignancies reported in BBW of all formulations.

Most members of this class are used for the treatment of rheumatic disorders, Crohn's disease and psoriasis with remarkable results in some of them, although not long-lasting and therefore requiring continuous treatment. Notably, not all diseases in which a relevant pathogenetic role had been attributed to TNF cytokines responded to specific TNF blockade (Sjögren syndrome, vasculitis, and Wegener granulomatosis). Moreover, the responsive diseases, such as RA, JIA, Ps, and CD did not equally respond to treatment, or to any agent of this class.

Although TNF cytokines were shown to play a role in a number of different disorders, such as those involving the cardiac function, CHF resisted or worsened after anti-TNF treatment. Notably, some unwanted effects could be bypassed by shifting to another member of the same drug class.

These differences within the same drug class were reflected also in the expression of other AEs.

Both Type A and Type B DRAEs were observed in this class, the most concerning categories being infections and malignancies consequent to the immunosuppressive activity of all class members. However, their expression, together with other relevant AEs, such as TB reactivation, hepatotoxicity, and induction of anti-drug antibodies varied in frequency and severity according to the agent used. In particular, TB cases appeared more frequently with mAb than with fusion proteins of the same drug class. In addition to the raise of anti-drug antibodies, formation of autoantibodies (ANA, anti-dsDNA) was also observed during anti-TNF treatment, which appears unexpected in the presence of the consistent immunosuppressive activity of this therapy. The concomitant reduction of Treg lymphocytes and consequent decrease of endogenous immunosurveillance have been evoked as a potential pathogenetic mechanisms of antibody response. Interestingly, the presence or entity of autoantibodies does not seem to correlate with increased clinical

signs of disease, and only a portion of positive patients showed associated syndromes, such as LLS.

Negative synergic effects were also observed when employing biomedicines combinations, such as TNF-inhibitors and anakinra (IL-1Ra antagonist), which brought to recommend avoidance of such association. However, the convenience of administering combined therapies for blocking two targets remains a debated issue. For example, it is not clear if the double action by two different biomedicines individually targeting VEGF, for inhibition of tumor vasculature, combined to those killing specific tumor cells, significantly increases efficacy or the insurgence of ADEs. Since the APRIL-dependent pathway is considered important for lupus nephritis, attempts to double block BLys and APRIL though the association of belimumab with atacicept, have been performed. Unfortunately, such attempts have produced a remarkable increase of serious infections, leading to an anticipated termination of the study (see belimumab, Chap. 9).

Although the effective increase of malignancies deserves conclusive data, the overall trend of this class is in favor of the existence of such risk, although not particularly related to length of treatment.

The effect of anti-TNF therapy on MS or other demyelinating disorders is controversial, given the alternate responses to therapy. Furthermore, insurgence of new demyelinating disorders, including MS, during therapy with anti-TNF inhibitors for rheumatic diseases (RA) was also observed.

The introduction of pegylated, Fc deprived mAbs, such as certolizumab, has contributed in understanding the typology of AEs derived from Fc immunogenicity and from its capacity to activate CDC and ADCC immune effector functions, which apparently are not crucial for therapeutic efficacy [24–26].

Overall, differences in the TNF inhibitors' capacity to induce adverse events and their relation to molecular structure or binding affinity, still need to be clarified, and will eventually contribute to future formulations of agents with better risk/benefit balance.

58.2.2 T Lymphocyte Inhibitors

T cell blockade was first attempted with polyclonal anti-lymphocyte and anti thymocyte sera to control rejection of solid organ transplants, leading to the development of the first monoclonal antibody licensed for human therapy, muromonab. This anti-CD3 agent produced a potent inhibition of the whole T cell compartment expressed by a profound immunosuppression, which successfully controlled allograft rejection, but generated an entire set of serious AEs as a consequence of immunosuppression and mainly of the strong immunogenicity of this fully murine mAb. The important learned lesson from muromonab was that monoclonal antibodies could be very effective but dangerous, and indicated the main road for future development: individuate more selective targets and cut down immunogenicity.

The subsequent products, such as basiliximab, daclizumab, and the fusion proteins abatacept, alefacept, and ustekinumab followed such strategy. Daclizumab and basiliximab were directed at CD25, a basic component of IL-2R, inhibiting the immune response and thus allowing the control of graft rejection. The spectrum of AEs was reduced, possibly because the CD25 target is structurally incapable of transmembrane signaling, behaving as an inert surface component after the specific mAb binding.

Infections appeared as more localized to the urinary and respiratory tract, especially in patients with a COPD history, and opportunistic infections were virtually absent. Abatacept induced a slight increase of infections and a lighter overall safety profile. By contrast, alefacept, binding to the CD2 component of LFA-3, interfered with T cell activation causing profound and persistent lymphopenia, serious infections, and malignancies in over 1 % of cases within the first 24 weeks of observation. This framework was associated with a rather low response to treatment (30 %), indicating the relevant role of LFA-3 pathway inhibition in the induction of adverse events. Alefacept was discontinued in 2011, and a supportive program was provided up to March 2012.

Ustekinumab expressed a general immunosuppressive activity, blocking IL-12 and IL-23 shared by activated T cells, NK cells, and other immune accessory cells. This caused an increase in the risk of infections and malignancies, although sparing some immune cells (naive T cells, Th1, Treg) and cytokine production from memory CD4+ cells, thus indicating the existence of different roles of cell subsets in tumorigenesis and/or the presence of alternative pathways yet to be identified. Nonetheless, a better dissection between inhibited and spared immune functions was more evident, and produced encouraging and protracted results, yet showing a considerable induction of AEs.

The long-lasting depleting effect on T cell produced by some of these biomedicines remains to be explained. In a study on RA patients CD4+ T cells and NK cells were still below normal levels after 12 years from treatment. This phenomenon, together with an unbalanced reconstitution of lymphocytes subsets after treatment with some mAbs, possibly leading to autoimmunes disorders, eems to be peculiar of these biomedicines (see for example alemtuzumab, Chap. 7).

Overall, inhibition of T cell functions greatly improved the control of allograft rejection, and showed considerable effects in some rheumatic diseases, but indicated their essential role in immune defense. When comparing the safety profiles of biomedicines affecting more than one immune cell lineage (alemtuzumab, tocilizumab, natalizumab), with more selective agents targeting a single cell lineage (rituximab, belimumab, alefacept, muromonab) or even a cell subset (brentuximab), some improvement in the safety profile could be noticed, although not much influencing the quality of BBW issued within the whole group, and confirming the pivotal role of T cell inhibition in the generation of most serious AEs. Nonetheless, it also showed, yet with uncertain results, the possibility of dissecting the specific T-dependent immune reactions to be inhibited. This could represent an intriguing strategy for future developments [27, 28].

58.2.3 B Lymphocyte Inhibitors

B cell inhibition and elimination are considered crucial for antibody-based auto-immune disorders, and for B cell leukemia and lymphoma. It is expected that such selective interventions expose to less risks than using anti T lymphocytes, since antibodies are only one terminal arm of the complex immune defense. In fact, primary selective immunodeficiencies have shown that the impairment of antibody production is less crucial than T-cell depletion, since most regulatory and effector functions of the immune system are based on T lymphocytes efficiency.

The major class of B cell inhibitors is directed to CD20, a virtually exclusive antigen at B lymphocyte cell surface. Rituximab, ibritumomab, ofatumumab, and tositumomab are all directed to this antigen and therefore they represent, together with anti TNF-inhibitors, the most furnished drug class of biomedicines.

As expected, infections (15–37 %) were common as mild to moderate event (about 80 %), with a relatively low rate (5–10 %) of serious and opportunistic forms, despite the prolonged depletion of B cells. Infections were mostly extra-cellular bacterial infections, since antibodies have a particular efficiency against them, while T lymphocytes are essential for intracellular infections of bacterial, viral, and fungal origin. Interestingly, the level of circulating immunoglobulins was moderately reduced but remained stable during treatment. Notably, mature plasma cells do not exhibit CD20 on their surface, although this condition does not fully explain the Ig production duration in long-term treatments, nor can be totally reassuring about late AEs, including the risk of insurgence of malignancy, for which longer observations are still needed. However, some concerning signs of an inefficient antibody protection emerged, such as virus reactivations including HBV and JC virus, the latter leading to insurgence of PML. Despite specific antibody suppression, hypersensitivity reactions were observed, particularly at first infusions, with possible multifactorial immune and non-immune mechanisms taking place in concomitance. The response to some no-live vaccines was reduced.

A more selective inhibition was obtained with omalizumab directed exclusively to IgE. This monoclonal acted also as proof of concept on the role of IgE in severe asthma, in a portion of chronic urticaria, and parasitic infections. In the latter case, no dedicated studies were available, but in particular geographic areas (Brazil) over 50 % of treated patients showed at least one helminth infestation. Despite humanization of this IgG1k mAb, hypersensitivity reactions including anaphylaxis, as early or late event, were observed. Malignancies (mainly solid, including parotid tumors), serious systemic eosinophilia, and serum sickness (presumably generated by IgE/omalizumab complexes) were also observed, once again confirming the crucial role of IgE in their control. Interestingly, two unexpected events were also observed during omalizumab therapy which both raising concerns and possibly indicating additional functional roles of IgE: elevated levels of myeloid cell counts after 29 month treatment, being normal before therapy and recovering after discontinuation; a cluster of constitutional new signs in an off-label treatment, including sleep disturbance, vertigo, exercise intolerance, myalgia,

joint pain without effusion, crippling fatigue, and feebleness, all gradually disappearing after omalizumab discontinuation [29].

Overall, the B-dependent safety profile, appeared more selective than the T-dependent profile, but revealed as much serious expressions, mainly when targeting CD20 molecules.

58.2.4 VEGF Inhibitors

In this class there are two monoclonal antibodies, bevacizumab and ranibizumab, and one fusion protein, aflibercept, which are used in oncology (bevacizumab, aflibercept/Zaltrap), and in the treatment of AMD (ranibizumab, aflibercept/Eylea, and bevacizumab as off-label intraocular administration).

The anti-angiogenic effect of these biomedicines used systemically (IV) or locally (IVI) produced significant general and local AEs, mainly as Type A reactions related to the expected toxicity at endothelial level, and mostly represented by bleeding disorders at both levels. Serious and sometimes fatal hemorrhages were observed mainly at gastrointestinal level with aflibercept/Zaltrap and bevacizumab, followed by ATE/VTE in various districts, including CNS.

However, some unexpected events—apparently related to vascular toxicity—also occurred, such as RPLS with aflibercept and bevacizumab, now considered a local form of CLS, or ONJ with bevacizumab (and aflibercept in the postmarketing setting). In the latter case, the damage at vascular level was questioned as pathogenetic, while the delay in wound healing appeared more in line with the anti-angiogenic effect of these biomedicines and with the presence of VEGF on fibroblasts.

Neutropenia and infections were less expected as drug-related AEs due to anti-angiogenic effect, although VEGF was observed on macrophages.

IVI administrations produced local hemorrhagic events, together with endophthalmitis, retinal detachment, ATE, increased intraocular pressure and local injection-related events. However, systemic complications in addition to non-ocular hemorrhage, such as sepsis, pneumonia, and gastrointestinal disorder were also observed. Notably, systemic AEs occurred also after IVI administration mimicking IV administrations, although to a lesser extent [30–32; see also aflibercept Chap. 42].

58.2.5 Cytokines

As previously mentioned, cytokines are a complex of heterogeneous factors both for structure and function, and therefore they cannot be considered as a unique drug class when considering their capacity of inducing AEs. As for their therapeutic use and related consequences, their functional classification (Chap. 48) seems more appropriate, although some structural peculiarities are relevant for the

understanding of their potential immunogenicity. The overall scenario of AEs is complex as well, but not surprising, since a number of them exert pleiotropic functions, and may behave differently according to their dose and their reciprocal systemic interactivity. The overall more peculiar expression of their action may be summarized in the induction of systemic syndromes, as described in Chap. 3, and their functionally related consequences.

After initial attempts with pro-inflammatory interleukins in cancer therapy, IL-1, and IL-2 studies were discontinued for their heavy safety profile. Two subsequently developed recombinant IL-2 (aldesleukin, denileukin-diftitox) are currently available, yet not extensively used.

IL-1 was associated with a modest antitumoral activity, and a concerning stimulatory effect on the hemopoietic stem cell compartment. IL-2, the first recombinant cytokine introduced in human therapy, was shown to exert a potent stimulatory effect on CD8+ lymphocytes and on NK cells. Due to the insurgence of relevant systemic AEs—mostly represented by CRS, CLS, and related complications—that rapidly limited the use in vivo, these interleukins resulted more successful as ex vivo expanders of hemopoietic stem cells, and for the production of autologous LAK cells, in association with other interleukins and growth factors.

These studies were also instructive for the understanding of pyrexia and of an entire cohort of symptoms caused by IL1 administration, such as arthralgia, myalgia, and hypotension resistant to indomethacin. The safety profiles of IL-1α and IL-1β were substantially similar.

IL-2 related AEs were dose-dependent and long-term treatment showed additional signs such as diffuse edema, thyroid dysfunction, and musculoskeletal algia.

Aldesleukin, a recombinant IL-2 approved by FDA (orphan drug designation for EMEA) for the treatment of metastatic renal carcinoma and melanoma, has a paradigmatic and heavy multi-organ safety profile including a series of exacerbations and new onset of autoimmune disorders. Notably, immunogenicity as revealed by the raise of non-neutralizing antibodies was frequent (70 %).

Denileukin-diftitox, a recombinant IL-2 fused to DT has a complex safety profile in which the toxic actions of distinct components are difficult to evaluate.

For the purpose of the present work, the safety profile of a non-glycosylated form of IL-11 has been considered within the group of hemopoietic stimulatory factor, because of its specific activity on megakaryocytes.

Interestingly, a new glycosylated formulation of IL-7 (CYT017), recently designated as an orphan drug for the treatment of PML, has shown to promote T cell expansion preferably of effector memory cells, without effects on other T cells, B cells, and NK cells, with consequent immune recovery without significant toxicity [33, 34].

58.2.6 Interferons

Alpha and beta IFNs are widely used in human therapy, and their safety profile includes neuropsychiatric disorders hypersensitivity reactions, cardiac and cerebrovascular disorders, multiorgan, and bone marrow toxicities. A common trait of this drug class is FLS of different severity (see CLS, Chap. 3), which appears to be dose-dependent. Autoimmune disorders appear also of particular interest, not because of their frequency but for their wide typology, including hematologic disorders (AIHA, ITCP) endocrinopathies (hyper- hypothyroidism, diabetes), MG, GBS, and systemic autoimmune disorders (SLE, RA, and hepatitis). The spectrum of safety was similar in standard and pegylated form of IFN, with a trend to produce a higher incidence of AEs and related discontinuations in the latter, but with no difference in neuropsychiatric events. Notably, their frequency tended to decrease over time.

When observed in detail, some differences appeared among various preparations of IFN. For example, in a large one head-to-head investigation comparing two IFNβ formulations, Rebif® and Avonex®, only the former induced rare cases of anaphylaxis, fulminant autoimmune hepatitis, Stevens-Johnson syndrome, erythema multiforme and cardiac disorders all considered as drug-related, while FLS and depression appeared more frequently with the latter.

Gamma IFN, or immune interferon, is a different molecule, although the safety profile was similar to other IFNs.

The peculiar necrotic skin reactions after subcutaneous IFN administration have been previously mentioned (see Chap. 52, p 555, and ref 21–23).

58.2.7 Hemopoietic Stimulatory Factors

Erythropoietic factors (epoetins) and myelopoietic stimulatory factors, which are usually considered as separate drug classes, have different safety profiles.

Epoetins increase the risk for multiorgan thrombotic events, tumor progression or recurrence, and death. Additional relevant AEs include hypertension, seizures, PRCA, and serious allergic reactions. Overall, hypertension, thrombotic events, and seizures in children were the most frequent occurrences together with allergic reactions. Anti-erythropoietin antibodies were also observed, but they were not neutralizing against endogenous and exogenous factors. PRCA was of special concern although appearing rarely, and was correlated with resistance to therapy and with the presence of specific antibodies.

Pegylated forms of epoetins, such as the synthetic peginesatide showed a similar safety profile, although with a trend to induce more renal failures, and anemia, but with a lower tendency to raise anti-erythropoietin antibodies with respect to recombinant formulations.

Particular concern in the treatment of cancer patients raised the observation that epoetins have stimulating effects on neoplastic cells, possibly related to their

activity on the JAK/STATs downstream pathways, although with contrasting time-related effects (see erythropoietins, Chap. 53). These concerns led to launch of a safety program on the use of these products in cancer patients (ESA APPRISE).

Myelopoietic stimulatory factors include a series of recombinant molecules exerting powerful stimulatory activity on stem cells (CSF, SCF) and on granulocyte/monocyte cells in various stages of maturation (G-CSF, GM-CSF). Their overall safety profile includes allergic reactions, splenic rupture, alveolar hemorrhage/hemoptysis, sickle cell disorders, and vasculitis as the more representative events. Moreover, cytogenetic abnormalities and transformation in MDS and AML were observed in pediatric patients with congenital neutropenia, deeply influencing the safety profiles. For example, ARDS due to sequestration of granulocytes in the pulmonary district, and CLS with related fluid retention after sargramostim administration were preferably observed in hematological malignancies, while renal and hepatic dysfunctions were more frequent in patients with precedent history of organ disease. Skin disorders were particularly elevated in AML patients compared to controls, with a statistically significant difference. However, overall variations in the AEs profiles rather concerned their frequency than their typology.

A distinct position is reserved to the thrombopoietic stimulatory factor, oprelvekin, a non-glycosylated form of IL-11, and possibly to a less known recombinant IL-11 manufactured in China. Oprelvekin safety profile consists of allergic reactions including anaphylaxis, CLS and related fluid retention including pulmonary edema, dilution anemia, cardiovascular and cerebrovascular events, papilledema, and renal failure. Among serious events there are pyrexia and neutropenic pyrexia, syncope, atrial fibrillation and diarrhea, all consistently higher than in controls. New formulations of IL-11 are in progress with the aim of reducing AEs and preserve therapeutic efficacy. Among these, a genetically modified formulation showed in fact a lower incidence and a milder profile of undesirable events than the reference oprelvekin preparation. Recently, a potentiated IL-11 fusion protein (hyper IL-11) was developed, and showed to be more stable and effective at lower doses, thus promising to have a better risk/benefit balance.

Finally, a potent stem cell stimulatory factor, ancestim, acting in association with other hemopoietic growth factors, is used in vivo only in some Countries, while it has a larger use for ex vivo stem cell expansion. The limited experience in vivo showed severe allergy and asthma in cancer patients including frequent (92 %) injection site reactions, cardio-respiratory disorders. Overall, the safety profile was similar to that of filgrastim.

58.2.8 Epidermal Growth Factors

The major concern with EGFs is the relevant potential stimulation of tumor growth experienced with the two available formulations, palifermin for IV administration, and becaplermin for topical use, which is an important limitation for their use in

oral mucositis induced by myelotoxic chemotherapy, and for lower extremities diabetic ulcers, respectively. Palifermin, employed as systemic treatment, induces also frequent signs of skin and mucosal toxicity. Becaplermin, although used topically, is able to increase the incidence of solid tumors (even distant from the site of application) and to raise the cancer death rate in patients using more than three tubes of the gel formulation.

In conclusion, the methodological methodological approach proposed in this chapter is more meant to suggest the need of building up a framework useful to untangle the complex panorama of adverse events to biomedicines, more than attempting a systematic organization of this recent intricate, and galloping area of medicine.

Some drug groups already have a few products to justify a comprehensive class analysis, but many of them only include one or two, that are on the market from too short a time to even start drawing conclusions. Nonetheless, being aware of such limitations, the proposed attempt may be of some help for a better understanding of the accumulated experience on AEs to biomedicines, while waiting for more solid information to come.

The major difficulty in evaluating the safety profile of a biomedicine relates to their frequent use in combination with other therapeutic agents, often composed of multiple associations of drugs sometimes capable of inducing heavier AEs.

The major difficulty in evaluating AEs within each drug class of biomedicines is the substantial lack of head-to-head studies. In a recent (March 2012) updated Drug Class Review from the Health and Science University of Oregon evaluating efficacy and safety of mAbs and fusion proteins in RA, only 18 direct comparative studies, almost exclusively observations studies, provided direct evidence of the AEs association with such treatments. On the other hand, over two hundred randomized controlled trials provided indirect comparative data. Moreover, the mentioned report stressed the particularly limited experience in pediatric patients, and the consequent lack of adequate data. These features are paradigmatic for the whole class of biomedicines [13].

Finally, an important approach for practical purposes consists in assessing safety profiles of biomedicines for the treatment of a single pathology. As an example, a recent attempt has considered the safety profiles of TNF inhibitors—anakinra, tocilizumab, abatacept, and rituximab in patients with RA.

All these agents gave considerable results in this disease, but showed a number of safety concerns that make difficult to evaluate the risk/benefit balance when deciding the strategy to be adopted in each patient. However, they showed that some of them could be avoided/mitigated by changing drug class or even substituting agents of the same class.

One crucial aspect relates to evaluation of short versus long-term safety issues in determining the appropriate therapy, and consequent strategies to be adopted for prevention and monitoring AEs during the course of therapy with biomedicines. From this kind of analyses, two sets of recommendations have been produced. In particular, one relates to prevention and diagnosis of infections, and one

specifically addresses TB infections, before, during, and after therapy in RA patients [35]. A similar procedure is advisable for other pathologies where a sufficient number of biomedicines are already available.

The drug class approach has relevant bias because of the experienced unpredictability of AEs expression among biomedicines. Nonetheless, when approaching new-marketed products—with a limited experience accumulated on a few trials on highly selected patients—drug class comparisons become essential and represent a unique support for such narrow experience to define better strategies for prevention, monitoring, and management of the expected "stone guest."

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